CLINICAL AND PHARMACOLOGICAL STUDIES WITH GUANETHIDINE IN THE TREATMENT OF HYPERTENSION

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NEW drugs for the treatment of hypertension now appear so rapidly that it is scarcely possible to evaluate one before it is superseded by another for which some additional virtues are claimed. Fortunately there are clinical and pharmacological criteria that can be applied to any of these drugs which make evaluation and comparison with other agents much easier. To be of real use a new drug must be specific in its pharmacological activity and have a consistent and dependable clinical effect. A drug which satisfies these requirements should preferably be fully absorbed after oral administration in a predictable time; there should be no significant tolerance to repeated administration, and undesirable side-effects should be slight. It is no longer enough to show that a drug will reduce blood-pressure, since there are already many drugs that will do this.

Recently two important new drugs have appeared that have an apparently specific action on the sympathetic nervous system and thereby allow reduction of blood-pressure without some of the miseries associated with the blockade of autonomic ganglia. These drugs, bretylium tosylate ('Darenthin') and guanethidine sulphate ('Ismelin'), have very similar pharmacological properties, but in clinical practice there are important differences. Bretylium proved disappointing because of irregularities in its action and a high incidence of tolerance (Dollery et al. 1960a and b). Reports so far published indicate that guanethidine is a powerful pressure-lowering drug which does not produce tolerance (Page and Dustan 1959, Leishman et al. 1959). These studies have encouraged us to give guanethidine to a group of patients similar to that treated with bretylium in our previous trial. So far there has been little information about the absorption, excretion, and metabolism of the drug and we have therefore studied these aspects.

Clinical Observations

Eighty patients were treated with oral guanethidine over a period of 9 months. They had very severe hypertensive disease, over half having had retinal hæmorrhages, exudates, or papillœdema. Many hazards attend the reduction of blood-pressure in the older patients, particularly those with vascular disease of the brain or heart, and we have preferred to have them under continuous observation until the correct dose has been found. Over three-quarters of them were therefore admitted to hospital for stabilisation on guanethidine. Patients with papillœdema are regarded as medical emergencies, requiring immediate reduction of pressure under hospital supervision. After discharge from the ward, patients are seen at first weekly in a special clinic and then at gradually increasing intervals. A summary of the different diagnostic categories is given in table I.

The results of treatment are indicated in table II. Control of the blood-pressure has been classified as "good" and "fair". Patients whose standing blood-pressure was 160/100 mm. Hg or lower on most occasions were regarded as having "good" control. Thirty-four (42·5%) of the eighty patients fell into this category. Patients whose diastolic blood-pressure was reduced at least 20 mm. Hg by guanethidine were regarded as having only "fair" control. There were thirty-four (42·5%) in this group. This figure may be misleading for it includes twelve (15%) patients with undoubted cerebral or myocardial ischæmia in whom only a moderate reduction of blood-pressure was desirable. It also includes a few patients with malignant hypertension whose clinical improvement was excellent although their blood-pressure levels were still such as to exclude them from a "good" result by the rigid criteria adopted. Four patients (5%) suffered such severe hypotension in the morning, and on effort, when their blood-pressure control was "good" that the dose had to be reduced to a level on which there was only "fair" control in the later part of the day. These have been listed separately in table II. There were eight patients in whom treatment was regarded as a failure, two because of drug resistance, two because of tremor, and two because of depression. Another patient had toxæmia of pregnancy: her blood-pressure was not well controlled but she was delivered of a live premature infant before the largest doses were reached. The eighth was a strong-willed woman who preferred pempidine and began to take it again on her own initiative after an episode of mild hypotension on guanethidine. All eight have been listed as failures of treatment. Most patients who had been treated previously with ganglion-blocking drugs expressed a strong preference for guanethidine.

TABLE I—PRIMARY INDICATION FOR LONG-CONTINUED TREATMENT OF PATIENTS WITH GUANETHIDINE

Diagnosis	No. of patients
Malignant hypertension (papillœdema)	19
Hypertension with retinal hæmorrhages and exudates	24
Hypertension with left ventricular enlargement	24
Hypertension complicating chronic renal disease	11
Hypertension in pregnancy	2

TABLE II—RESULTS IN 80 PATIENTS TREATED WITH GUANETHIDINE

—	No. of patients	% total
Good control of blood-pressure (standing B.P. 160/100 or lower on most occasions)	34	42·5
Fair control of blood-pressure (at least 20 mm. Hg reduction in diastolic B.P.)	34*	42·5
Severe exercise hypotension limiting control of resting pressure	4	5·0
Failure of treatment	8	10·0

* Of these 12 (15%) had cerebral or myocardial ischæmia and only a moderate reduction of blood-pressure was desirable.

The doses used ranged from 10 to 750 mg. daily, but most patients have required between 30 and 120 mg. daily. Only three patients reached a dose of 300 mg. and all had severe disease with retinitis or papillœdema. Since guanethidine has a cumulative action we found it best to allow 3 days between alterations of dose so that a steady effect was reached. Treatment was started with a dose of 30 mg. daily: this is larger than that recommended by Leishman et al. (1959) but smaller than that usually employed by Page and Dustan (1959). This appears to be a reasonable compromise, for only a few patients require less, and if very small increments are used it may take a long time to reach effective doses. Usually increments of 30 mg. daily were added at 3-day intervals, although larger increments were used if it became obvious that high doses were required. We should emphasise that this regime was designed for use with patients in hospital, and such rapid increases in dose would be inadvisable with outpatients unless they were seen daily.

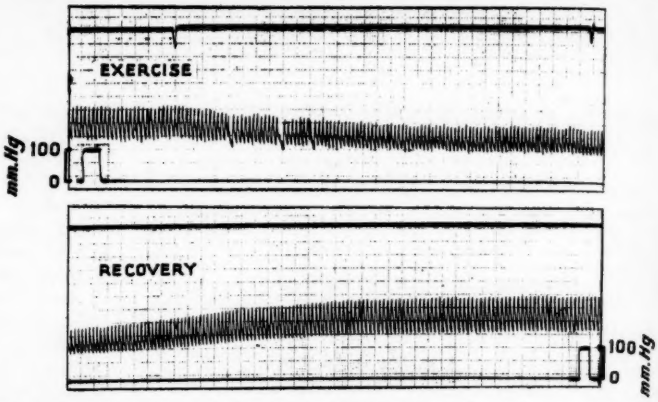

Fig. 2—A continuous record of the lying blood-pressure of a patient treated with guanethidine during, and immediately after, exercise.
The patient exercised the legs for one minute (markers on the upper trace). The two traces follow one another directly.

CHARACTERISTICS OF THE FALL IN BLOOD-PRESSURE

Postural Fall

The pressure-lowering action of guanethidine is a result of blockade of the sympathetic vasomotor system, and the fall in pressure is greatest when the patient is upright. Our aim was to achieve normal, or near normal, pressures in the standing position. Naturally the lying blood-pressure was higher, and often much higher, than the standing blood-pressure. Patients with malignant hypertension were nursed in hospital with the head of the bed raised on 12 in. blocks; if they had early-morning headaches they were advised to use blocks at home.

Diurnal Variations

Many patients noticed that they felt giddy and faint if they had to get up in the night or on first rising in the morning. Observations in hospital confirmed that the reduction of blood-pressure was greatest when the patient first rose from bed. We could not prevent this symptom by altering the times of doses. At first we used three equally spaced daily doses, but as this seemed to have no advantage all the tablets were given at breakfast time. Even 24 hours after the previous dose a number of patients were greatly incapacitated in the early morning. Some complained of great weakness, others had syncope while washing, and two could not raise their hands to their faces to shave. In the four patients most severely affected by morning hypotension reduction of dosage led to relief, but this meant accepting poor control of blood-pressure in the later part of the day. An evening dose of pempidine may be needed.

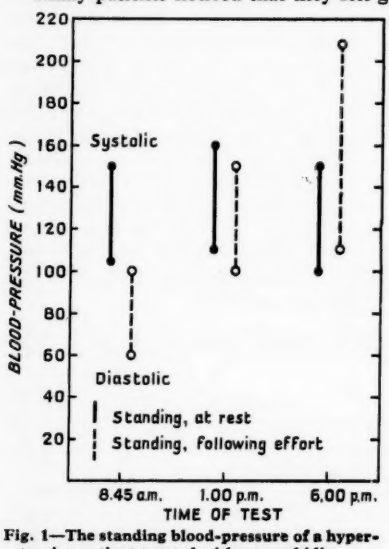

Fig. 1—The standing blood-pressure of a hypertensive patient treated with guanethidine as a single daily dose at 9 a.m. before and immediately after a standard exercise test in the morning, at midday, and in the evening.

Exercise Hypotension

A fall of blood-pressure on effort, noted already with bretylium (Lowe and Rosenheim 1960), has been prominent with guanethidine. This has an important practical and theoretical interest. Patients may become almost syncopal during exertion. This happened most often to patients who, even without effort, have had hypotensive symptoms in the early morning. One patient felt faint when running for a bus on the way to work, another on climbing stairs in the underground. Three patients with these symptoms were studied in hospital and some diurnal variation in the fall of blood pressure on exertion was found. The most striking example is shown in fig. 1. A 59-year-old man was kept in bed all day except for the three occasions when he performed a standard exercise test which involved climbing two flights of stairs and walking 100 yards. In the morning his pressure fell after this test and he felt " swimmy ", but in the afternoon his pressure actually rose after the same exertion. After the blood-pressure falls on effort in this way it begins to return to its previous level within $^1/_2$–1 minute of the end of exercise and within 2–3 minutes it often rises to a value slightly higher than that before the exercise. The fall of blood-pressure on exertion is not confined to the standing position and we obtained some striking falls when patients were exercised lying flat. A continuous record of blood-pressure during such exercise is shown in fig. 2.

A 55-year-old woman exercised her legs for one minute while lying flat, and the blood-pressure was continuously recorded from a needle in the brachial artery. During the exercise period the blood-pressure fell continuously from 230/130 mm. Hg to 165/85 and then rose again rapidly to reach a value of 255/135 a minute after exercise stopped. In four of the five patients who were exercised lying flat

the blood-pressure fell and then rose again to a slightly higher pressure after the end of exercise.

SIDE-EFFECTS OF GUANETHIDINE

A great variety of side-effects was noted. Most of these were similar to those already described with bretylium, although the emphasis was quite different. The side-effects were not usually severe and less than a third of our patients had more than trivial symptoms.

Diarrhœa

Most patients passed only semiformed stools even if they did not complain of diarrhœa. Often patients who had become accustomed to severe constipation from ganglion-blocking drugs seemed to welcome having two or three bowel actions in the day. A number had frank diarrhœa and six patients had ten or more motions in the 24 hours. The milder cases were treated with a kaolin mixture and the severer with 2·5 mg. of pempidine twice daily. The addition of this small dose of pempidine usually had little effect on control of blood-pressure but was most effective in controlling the diarrhœa.

Bradycardia

Bradycardia was noted in many patients having guanethidine, but it only gave rise to anxiety when the patient was digitalised. One patient who had had hypertensive heart-failure was discharged having 60 mg. of guanethidine and 0·5 mg. digoxin daily. As an outpatient she was found to have a pulse-rate of 35 beats per min.; the rhythm at this time was not established. When digitalis was stopped her pulse-rate increased to 60 beats.

Parotid Tenderness and Nasal Obstruction

Both of these symptoms, which were prominent with bretylium, also occurred with guanethidine, but they were much less frequent. Four patients noticed facial tenderness in the parotid region, particularly while chewing. Two patients had nasal obstruction and in one it was severe enough to interfere with sleep. He obtained some relief from an ephedrine inhaler.

Tremor

Six patients treated with guanethidine developed a coarse muscle tremor which involved both limbs and trunk. In two of them the tremor was severe and muscle fasciculation was also noted: both patients gradually improved over 2 weeks after the withdrawal of the drug.

The tremor may result from a central action of the drug, but the muscle fasciculation suggests a direct action on the motor neurones or the striated muscle itself.

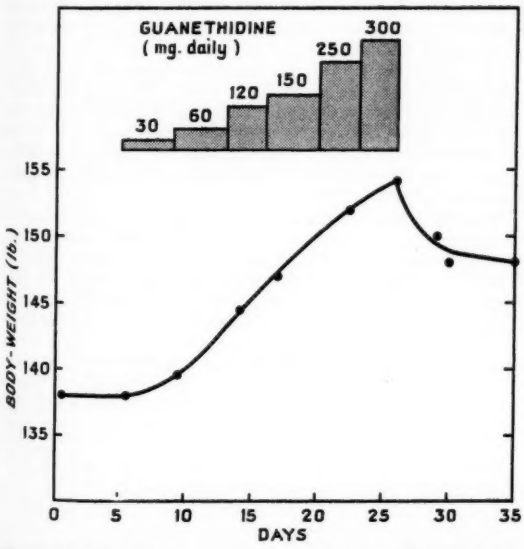

Fig. 3—The weight of a hypertensive patient who gained 16 lb. during 20 days' treatment with guanethidine and developed congestive heart-failure.

Fluid Retention and Congestive Heart-failure

Other workers (Leishman et al. 1959) have noted weight gain and œdema with guanethidine, and this was also our experience. Daily weighing showed that many patients temporarily gained 2–3 lb. when they began to take guanethidine. Six patients gained 10 lb. or more (fig. 3) and four of them developed the clinical picture of congestive heart-failure with raised jugular venous pressure and peripheral œdema. Four patients had malignant hypertension with considerable renal impairment. It might be supposed that this effect was the result of a fall in glomerular filtration-rate following the fall in blood-pressure, but this explanation is unsatisfactory since one patient had no fall in blood-pressure or change in blood-urea and the pressures of two of the other three patients had previously been controlled with pempidine without the appearance of œdema. Sodium-balance studies were made in two other patients on a constant intake of 100 mEq. daily, but these patients showed neither weight gain nor sodium retention. The effect is clearly variable and as yet quite unexplained. It is interesting that our patients with œdema had the clinical picture of congestive failure but did not develop paroxysmal dyspnœa or basal crepitations although the chest X-ray demonstrated pulmonary venous congestion.

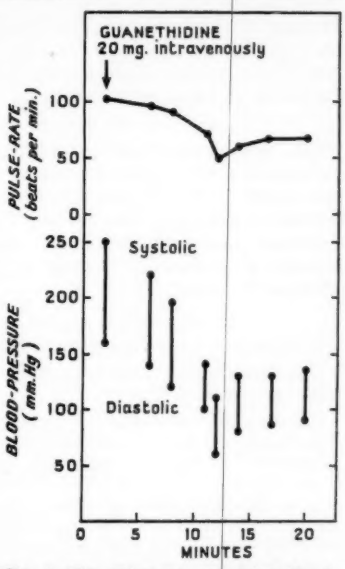

Fig. 4—The pulse-rate and lying blood-pressure of a patient with malignant hypertension and pulmonary œdema who was treated with a 20 mg. intravenous dose of guanethidine.

Breathlessness

Five patients complained of dyspnœa on exertion that occurred when pressure control was good and there were no signs of heart-failure. This symptom was paradoxical in that dyspnœa was worse after control of blood-pressure than it had been before. At first we suspected that this symptom was a manifestation of exercise hypotension, but although two patients had hypotension on exercise the other three had not.

Weakness, Tiredness, and Depression

These symptoms have been common. Some, of course, were neurotic symptoms encouraged by the careful attention given to patients' complaints. However, patients who complained most of lassitude had very low blood-pressures, particularly on exertion. One patient, who said he was "completely washed out", had a standing systolic pressure of 75 mm. Hg at rest. Complaints of weakness and tiredness have often occurred after reduction of blood-pressure with a variety of drugs, and they tend to improve as time passes. Two patients became severely depressed and had suicidal thoughts; both improved after the drug was withdrawn.

Failure of Ejaculation

We are uncertain how frequent this symptom has been, but six intelligent male patients mentioned it. Some unfortunates exchanged impotence with ganglion-blocking drugs for failure of ejaculation with guanethidine. Despite failure of ejaculation, orgasm was normal.

This lengthy discussion of side-effects should not hide the fact that both their incidence and severity were much less than with ganglion-blocking drugs and comparable with the incidence found with bretylium.

TOLERANCE

Once a good hypotensive effect has been achieved with guanethidine, subsequent alterations of dose have usually been small. There has been no evidence of the progressive increase in dose that was required with bretylium. After 9 months' experience it does not seem that tolerance to repeated administration is likely to be a major problem with guanethidine.

INTRAVENOUS ADMINISTRATION

Intravenous doses were given to fourteen patients either because the pressure had to be reduced urgently or during pharmacological studies.

The doses used ranged from 20 to 100 mg. although not more than 40 mg. was given as a single injection. Immediately after an intravenous dose the patients noticed a feeling of warmth in the skin and some of them had obvious flushing. There was often a small immediate rise in blood-pressure followed by a fall that was maximal 10–20 minutes after the injection. An excellent clinical response was obtained in a patient with malignant hypertension who had acute pulmonary œdema. The blood-pressure fell from 250/160 mm. Hg to 110/60 in 10 minutes and the pulse slowed from 100 to 50 beats per min. (fig. 4). At the same time dyspnœa improved dramatically. Although intravenous guanethidine appears quite satisfactory for urgent reduction of pressure, we have preferred to use subcutaneous pentolinium in most patients since its duration of action is shorter and more easily controlled.

Pharmacological Studies

Radioactive guanethidine, labelled with ^{14}C in the guanidine carbon with a specific activity of 0·67 μC per mg. was used. Doses of 5 μC were given orally to fasting patients and 2·5 μC intravenously to others. Urine was collected in 2-hourly periods for the first 12 hours and then a single 12-hour collection was followed by two 24-hour collections. A 3-day stool collection was made from four patients. Four studies were made with oral doses, three with intravenous doses. Urine samples were counted directly in 1 ml. aliquots in a liquid scintillation counter (Jones et al. 1960). Standards were counted with further urine aliquots to allow for errors due to quenching. Fæces were homogenised and a 12 g. sample homogenised with 120 ml. of N/10 NaOH. This fluid was centrifuged and divided into two equal parts, to one of which was added a known amount of labelled guanethidine. Each sample was extracted with 120 ml. of chloroform and after separation the guanethidine was re-extracted from the chloroform with 3 ml. of N/10 HCl. 1·0 ml. of the acid extract was counted. Rat tissue was homogenised and the protein was precipitated with trichloracetic acid. The supernatant fluid was made up to a standard volume and 1 ml. samples counted.

Chemical estimations of guanethidine were made using a dye-conjugation method. 0·5 ml. of neutral urine or fæcal extract was added to 10 ml. of pH 3·6 buffer with 4 ml. of 0·08 per cent bromcresol-green and the mixture was extracted with 4 ml. of chloroform. The dye complex in the chloroform phase was read at 410 μ in a spectrophotometer. Extracts of urine and fæces were made by chloroform extraction in the same way as for the radioactive samples. The chemical method was not ideal because there was an appreciable blank from normal urine or fæces. Further, the recoveries were rather low, ranging from 20 to 50% depending upon the relative quantities of water and chloroform.

STUDIES IN RATS

The first studies were made in rats, using the bromcresol-green dye-conjugation method for the estimation of guanethidine. The methyl-orange method (Brodie et al. 1945) was also tried

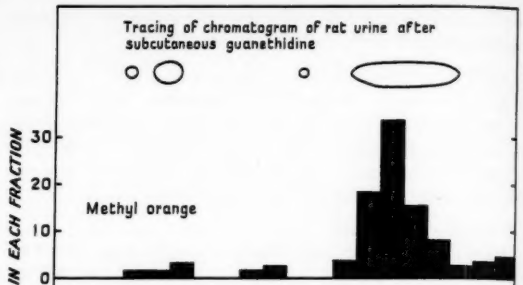

Fig. 5—A tracing of a chromatogram of urine from a rat given 20 mg. guanethidine subcutaneously.

The chromatogram was eluted in strips and each fraction was estimated by the bromcresol-green and methyl-orange dye-conjugation methods.

but was found less sensitive than that using bromcresol green. Rats were given 5 and 10 mg. doses of pure guanethidine subcutaneously and urine was collected for the following 24 hours. Chromatograms were made from undiluted urine specimens on Whatman no. 4 paper using isopropanol: concentrated ammonia: water, 200: 20: 30. The chromatograms were stained for guanidium compounds with the Dragendorf, Sakaguchi, diacetyl and iodoplatinate reagents. In most chromatograms three metabolites could be identified in addition to the main guanethidine spot (fig. 5). These metabolites are of unknown structure but they stain with reagents specific for guanidium and this suggests that the basic molecule of guanethidine is still intact. The RF value of guanethidine in this system was 80 and the main metabolite had an RF value of 23. Chromatography of large quantities of urine followed by elution and estimation by the dye methods showed that all three metabolites were determined by both methods in addition to the guanethidine itself.

The excretion of guanethidine in the urine after a 5 mg. subcutaneous dose was studied in a group of four acidotic and four alkalotic rats. The mean excretion of guanethidine in the first 4 hours was 0·64 mg. in the acidotic rats and 0·57 mg. in the alkalotic rats. The difference is not significant: this suggests that the excretion of guanethidine in the urine is not influenced by pH.

A group of four rats was given 5 mg. of guanethidine by stomach tube and urinary excretion of guanethidine was estimated over the following 24 hours. In only one case did the amount of drug excreted rise above the urine blank for the method: the animal excreted 9% of the dose in 24 hours. Poor absorption of these doses from the rat's alimentary tract was

TABLE III—DISTRIBUTION OF GUANETHIDINE IN THE TISSUES OF RATS

Tissues	Tissue/plasma concentration ratio	
	Radioactive method	Chemical method
Kidney	11·9	11·6
Liver	9·9	5·2
Lung	8·1	9·2
Heart	..	8·7
Spleen	3·4	3·1
Voluntary muscles	3·3	..
Brain	1·1	1·0

confirmed by comparing the amount excreted in the urine and the amount remaining in the gut 4 hours after a 20 mg. oral dose of guanethidine. In two rats there was respectively 8·2 times and 6·0 times as much remaining in the gut as was excreted in the urine during this time.

The possibility of excretion by routes other than the urine was examined in rats. Estimations of guanethidine in the bile after intubation of the common bileduct were made for 12 hours after a 5 mg. subcutaneous dose but only trace amounts were found. However, when the gut contents were estimated 13% of the administered dose was recovered. When the gut was ligated at the pylorus and the ileocæcal junction, approximately equal quantities were found in stomach, small intestine, and colon.

Tissue distribution studies were made by both the chemical and radioactive method. The highest concentrations were found in the kidney by both methods, and this was the only organ from which it was possible to isolate enough guanethidine to identify by chromatography. The tissue/plasma concentration ratios are given in table III. Premedication of rats with 10 mg. 'Darstine' did not alter the concentration of radioactive guanethidine in the kidney.

STUDIES OF PATIENTS

Preliminary studies using the chemical method showed that the amount excreted by patients in 24 hours after an intravenous dose was approximately 50%, and after an oral dose only about 20%. After oral doses approximately 60% of the dose could be found in the fæces but recoveries were very low and this figure must be regarded as very approximate. The radioactive method allowed much more precise measurements to be made. The amounts excreted in the urine after intravenous and oral doses are summarised in table IV.

TABLE IV—EXCRETION OF ^{14}C-GUANETHIDINE IN URINE AFTER ORAL AND INTRAVENOUS DOSES IN SEVEN PATIENTS (A–G)

Hours after dose	Percentage of dose excreted in each period						
	Oral doses				Intravenous doses		
	A	B	C	D	E	F	G
0–2 ..	0·57	0·04	2·32	5·04	21·19	13·86	15·96
2–4 ..	3·96	10·5	10·34	5·85	10·04	5·19	5·46
4–6 ..	2·19	5·9	..	1·8	8·01	3·96	5·08
6–8 ..	1·63	3·76	..	3·87	1·75	1·40	4·38
8–10 ..	2·06	2·3	6·24	1·6	5·86	2·40	3·88
10–12 ..	2·48	2·1	..	1·35	2·21	2·06	3·02
12–24 ..	3·93	4·7	6·73	3·7	12·97	13·80	12·12
24–48 ..	6·91	4·59	8·26	9·8	10·1	11·7	19·2
48–72 ..	3·78	1·69	5·51	8·1	6·0	5·3	8·3
24 hr. total ..	16·82	29·3	25·6	23·21	62·03	42·67	49·9
72 hr. total ..	27·51	35·58	39·4	41·1	78·13	59·67	77·40
24 hr. mean ..	23·7				51·8		
72 hr. mean ..	35·89				71·7		

The mean urinary excretion 24 hours after the dose was 52% when the dose was given intravenously and after oral doses it was 24%. By 72 hours after the dose the excretion had risen to 72% after the intravenous doses and 36% after the oral doses (fig. 6).

The excretion was rapid in the first few hours after an intravenous dose but appreciable excretion continued even 72 hours afterwards. When the drug was given orally the rate of excretion was low in the first 2 hours and rose to a maximum between 2 and 4 hours after the dose. Appreciable excretion continued even 72 hours after an oral dose (fig. 7). This slow excretion of the drug is probably relevant to its prolonged and cumulative action.

There was not enough radioactivity in the urine to determine whether all the ^{14}C was still in the form of guanethidine. However, the chloroform/water partition in alkaline solution was closely similar to that of the original guanethidine and all the radioactivity could be absorbed by activated charcoal. If the guanidium radical containing the labelled carbon were split off the heterocyclic portion of the molecule, urea would be the most likely compound to be formed. This would not be absorbed by activated charcoal. Guanethidine could be

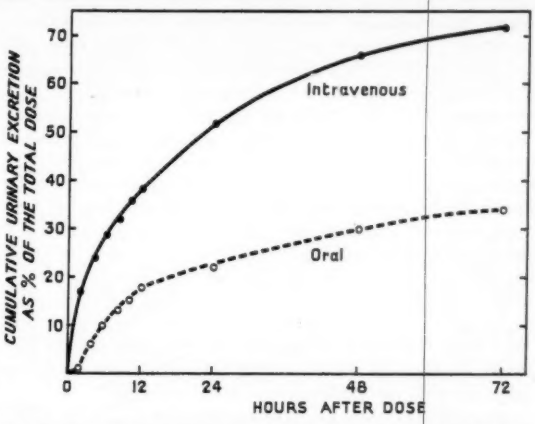

Fig. 6—The mean cumulative urinary excretion of ^{14}C labelled guanethidine over 72 hours from 4 patients given oral doses and 3 patients given the drug intravenously.

quantitatively recovered from blood after incubation for 24 hours and from fæces for up to 8 days. The findings suggest that guanethidine is stable in these biological materials, at least at neutral pH. The excretion of ^{14}C guanethidine in the fæces was measured over 3 days following the dose from three patients who were given the drug by mouth and one who had it intravenously. The total recovery of guanethidine from the fæces was 19%, 23%, and 26% in the patients who had oral doses. Only 3% was recovered from the fæces of the patient who had the drug intravenously. After oral doses enough guanethidine was present in the stool to be identified by chromatography. Specimens of bile from a patient who had a T tube in place after a cholecystectomy were analysed for 6 hours after an intravenous dose of guanethidine. Only trace amounts, too small for accurate estimation, could be found in the bile.

Discussion

We have found guanethidine a useful addition to drugs for the treatment of hypertension. It shares with bretylium the great advantage of not causing any parasympathetic blockade. Patients are therefore spared constipation, impotence, dryness of the mouth, and iridoplegia, and there is no risk of paralytic ileus. Further-

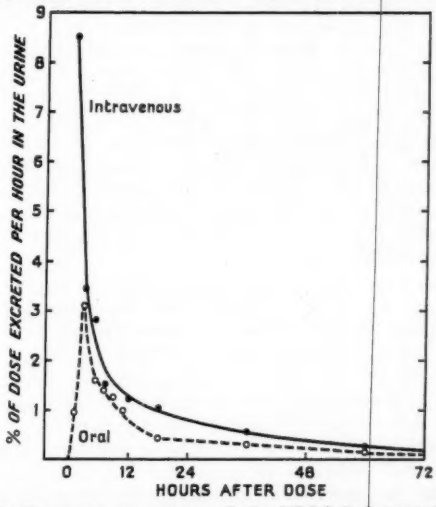

Fig. 7—The mean percentages of the ^{14}C-labelled guanethidine excreted per hour in the urine by 4 patients given oral doses and 3 patients given the drug intravenously.

more, guanethidine has advantages over bretylium, particularly in very severe hypertension, in that patients did not become resistant to the drug and the hypotension is less variable. These are substantial advantages, but management of the patient on this new drug still requires continuous skilled supervision. At best, sympathetic paralysis is a clumsy interference with the homœostatic mechanisms of blood-pressure regulation, and it is only justifiable because it can frequently save the lives of the most severely hypertensive patients. The reduction of blood-pressure is only really effective when the patient is upright and the lying pressure may return to very high levels. With the ganglion-blocking drugs the optimal reduction of pressure was achieved when the patient had mild symptoms of hypotension on standing. While this might be the aim with guanethidine, great care must be taken to avoid severe hypotension on exercise.

We learned that it was inadvisable to dismiss as neurotic patients' complaints of faintness and weakness, even in the face of high standing blood-pressures, without measuring the blood-pressure immediately after exercise. A patient with malignant hypertension came to the clinic complaining of morning weakness; his standing pressure at 10 a.m. was 220/130 mm. Hg. Despite his symptoms, his high blood-pressure indicated an increase of dose until he returned from climbing two flights of stairs and was found to have a standing blood-pressure of 90/40. A short exercise on stairs should be done on follow-up to gauge such an effect. Careful adjustment of the dose usually allowed a compromise to be reached between symptoms on exercise and reasonably good pressure control throughout the day, but the adjustment was often critical. In a few patients who did heavy manual labour, hypotension on effort seriously limited our ability to control their blood-pressure at rest with guanethidine. Fortunately, once a stable dose of guanethidine was found, later adjustments were small. As might be expected, chlorothiazide or mercurial diuretics potentiated the action of guanethidine but they were given only to patients with œdema. We prefer to use only one pressure-lowering agent where possible, and the blood-pressure of most patients was controlled by guanethidine alone.

There was no apparent difference in the response of patients with renal and essential hypertension. Patients with the severest forms of hypertension tended to need larger doses than those with milder forms. In patients who had retinal changes of grade 3 or 4 at the time treatment was started there has been a steady regression of hæmorrhages, exudates, and papillœdema. Three patients who were being treated with guanethidine died during the period of the trial, but all from uræmia. They were already uræmic at the time of diagnosis, and despite reasonably good control of pressure their renal function became steadily worse.

Apart from the tendency to low pressures in the early morning, the effect of guanethidine was fairly uniform throughout the day. When treatment was stopped there was a fall of blood-pressure on standing for as long as 4 days after the last dose. In many ways this prolonged action of guanethidine is an advantage because it allows a single daily dose to be used. Unfortunately it does not allow the fine adjustments that may be needed to counteract diurnal variations in pressure. The fall of blood-pressure on exercise is of considerable hæmodynamic interest but therapeutically it is a nuisance. Although most patients whose blood-pressures were well controlled had a further fall in pressure on exercise, a few did not. This effect is being further studied.

The main side-effects were diarrhœa and bradycardia, and neither interfered very greatly with treatment. When diarrhœa was very troublesome it could always be controlled with kaolin mixtures and small doses of pempidine. Symptoms such as nasal obstruction, parotid tenderness, and failure of ejaculation presumably reflect other aspects of adrenergic blockade, and at present they have to be accepted by patients as part of the price paid for the control of their blood-pressures.

Some patients gain weight and retain fluid while having guanethidine, and congestive cardiac failure may develop. This may need to be treated with diuretics. If digitalis is also used, the pulse-rate, already slow with guanethidine, may fall still further to rather worrying levels.

When labelled guanethidine was given by mouth to patients 36% was recovered from the urine in 72 hours. When it was injected intravenously the recovery was 72% in the same time. Recovery of orally administered guanethidine from the fæces was 20 to 25%; so about 40% of the dose is unaccounted for.

The distribution of guanethidine in the organs of rats was predominantly intracellular and the plasma concentration was low. The highest concentrations of guanethidine were found in the kidney; the lungs and liver contained slightly less. The brain contained a low concentration similar to that found in the plasma. The high kidney concentration of guanethidine is comparable to that found with other organic bases, such as guanidine and tolazoline (Peters 1960), but, unlike these compounds, guanethidine was not displaced from kidney tissue by ' Darstine '. We have no evidence of the proportion of guanethidine metabolised in man, but the chromatographic studies in rats suggest that it is small; the three metabolites identified on the chromatograms all retained the staining reactions of guanidium—evidence that structural modifications were slight.

Maxwell et al. (1960) have shown in normal and hypertensive dogs that the action of guanethidine may persist for up to 2 weeks. We have not observed such a long period of action in man, but excretion continues for at least 3 days, after either oral or intravenous doses, and the hypotensive effect can still be found for at least this time after withdrawal of the drug. Our studies suggest two possible mechanisms for this long action. In rats guanethidine is excreted into the gut, and it may then be reabsorbed and excreted again in a cyclical manner. However, the small recovery from fæces after an intravenous dose in man is against this explanation. Perhaps a more likely one is that guanethidine is slowly released from the organs of the body.

The advantages of guanethidine are freedom from parasympathetic side-effects and absence of drug tolerance. The major disadvantage is the possibility of profound hypotension during muscular activity, which can be avoided by a reduction of dosage but sometimes at the expense of good control of blood-pressure. Irregularity of blood-pressure control is particularly likely to be disadvantageous when there are symptoms of cardiac or cerebral ischæmia. Tremor and depression are important, though uncommon, side-effects.

Summary

Guanethidine has been given to eighty severely hypertensive patients over a period of 9 months in doses of 10 to 750 mg. daily by mouth. It has occasionally also been

used intravenously. Control of blood-pressure has mainly been satisfactory and retinopathy has steadily regressed. Three patients, already uræmic when diagnosed, died from renal failure despite adequate control of blood-pressure.

The fall in blood-pressure is greatest while standing, during exercise, and in the morning. Reduction of dosage to avoid the latter two effects may lead to imperfect control of blood-pressure at the end of the day. Tolerance is not a problem. There is no parasympathetic blockade, but there are several side-effects, diarrhœa and bradycardia being the commonest; fluid retention is occasionally troublesome; four patients developed severe tremor or depression.

Using chemical and radioactive-tracer techniques, the absorption, metabolism, and excretion of guanethidine have been studied in man and in rats. Absorption from the gut is incomplete, and excretion in urine and fæces is prolonged. Hardly any is excreted in the bile. Concentration of the drug is mainly intracellular, and is highest in the kidney. It is excreted in the urine both as unchanged guanethidine and as three closely related metabolites.

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COMPARISON OF BRETYLIUM TOSYLATE WITH GUANETHIDINE IN THE TREATMENT OF SEVERE HYPERTENSION

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IN this series our criteria for selecting the patients were those previously described (Platt and Sears 1956, Sears et al. 1959). Bretylium tosylate was used in 27 patients and guanethidine in 17, 6 of whom had previously been on bretylium tosylate. Of the 44 cases, 29 were judged to have malignant hypertension from the level of the diastolic blood-pressure and the presence of papillœdema. The remaining 15 all had severe benign hypertension with diastolic pressures of over 120 mm. Hg, and lesser grades of retinopathy. In several of these patients the retinopathy was progressive and they were probably in a pre-malignant phase. We have not included patients with mild hypertension having diastolic pressures below 120 mm. Hg. In fact, only 6 patients had diastolic pressures of 140 mm. Hg or less (see table I). The age range was from 17 to 65 years and the age distribution is shown in table II.

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TABLE I—DEGREE OF HYPERTENSION IN THE TWO GROUPS

Range of diastolic pressure (mm. Hg)	No. of bretylium tosylate cases	No. of guanethidine cases
120–130	1	1
130–140	2	2
140–150	13	4
150–160	6	3
160–170	3	2
170–180	2	3
Over 180	0	2

TABLE II—AGE OF PATIENTS

Age (years)	No. of cases on bretylium tosylate	No. of cases on guanethidine
10–20	0	1
20–30	3	1
30–40	6	1
40–50	6	6
50–60	12	7
Over 60	0	1
Total	27	17

Inpatient Stabilisation

All but 2 patients were admitted to hospital for stabilisation. As the majority had previously been treated with other drugs, usually ganglion-blocking agents, it was thought unnecessary in these cases to observe baseline blood-pressure readings for any extended time, as these were already known from previous observations. No particular restrictions were placed on the patients' activities during their stay in hospital: rest in bed was not enforced unless indicated for other reasons.

Bretylium tosylate was started in a dosage of 200 mg. three times daily, thirty minutes before meals, at approximately 7.30 A.M., 12.30 P.M., and 5.30 P.M. Guanethidine was initially started with 10 mg. daily doses, but later 20 mg. daily was the usual starting dose. In only 2 cases was the final dose below this, and it seems justifiable to recommend 20 mg. as a starting dose except in older patients, in special cases where it is particularly desirable to avoid hypotensive episodes, and in renal failure.

Lying and standing blood-pressures were recorded daily at about the same time. At the beginning of the trial, more frequent observations of the blood-pressure throughout the day confirmed previous findings on the duration of action of the two drugs (Boura et al. 1959, Leishman et al. 1959). As necessary, the dose of bretylium tosylate was increased by 100 mg. increments t.i.d. every two or three days until a satisfactory response was obtained. Because of its known cumulative effect, the dose of guanethidine was increased by 10 mg. increments at longer intervals. When we first used the drug, a period of five to seven days was allowed to elapse before a further increase was made. More recently, however, increases have been made at shorter intervals. This appears to be safe if the increments are small (5–10 mg.), and if the patient is watched closely for excessive postural hypotension.

Outpatient Supervision

All patients were seen within two weeks of discharge from hospital by one of us (H. T. N. S.) in a clinic exclusively concerned with the management of hypertensive patients. An attempt was made to see each patient at the same time of day at each attendance; the blood-pressure was taken three times, both recumbent and standing; and the lowest reading in each posture was recorded. A graph of blood-pressure readings was kept for each patient to facilitate assessment of response to treatment.

Results

Because of fluctuation in blood-pressure readings, it is difficult if not impossible to measure the success or failure of treatment by the achievement of an arbitrarily fixed drop in diastolic pressure. On the whole we aim at a standing diastolic pressure in the region of 100 mm. Hg, in most cases; but a patient with an initial diastolic pressure of 180 mm. Hg would be classified as responding satisfactorily if we achieved a drop in pressure to only 115–120 mm. Hg—particularly if there was a simultaneous improvement of retinopathy.

Thus, in assessing the response to treatment in each case we have taken into account improvement of symptoms, the fall in blood-pressures, and the change in retinal appearances, together with the patient's general condition. Development of severe side-effects in a patient whose blood-pressure was adequately controlled would be regarded as a failure of treatment. On this basis we have classified the results of treatment into three groups: satisfactory, fair, and poor. These are shown in table III both for the period of initial inpatient stabilisation and for the subsequent follow-up period, which has ranged from two to nine months.

TABLE III—RESPONSE TO TREATMENT

Response to treatment	Bretylium tosylate		Guanethidine	
	Inpatient	Outpatient	Inpatient	Outpatient*
Satisfactory	22	5	16	10
Fair	2	4	0	5
Poor	1	16	1	1

* Only 16 patients were discharged from hospital on guanethidine.

Of the 2 other patients whose treatment with bretylium tosylate started when they were outpatients, one responded poorly and the other satisfactorily with the addition of reserpine and chlorothiazide.

Illustrative Cases

Case 1.—Man, aged 44, with malignant hypertension; blood-pressure 280/170 mm. Hg and blood-urea 100 mg. per 100 ml. He was changed from pentolinium and reserpine to bretylium tosylate last October and was discharged from hospital taking 300 mg. t.i.d. which produced a good postural drop in blood-pressure. In the outpatient clinic, in spite of gradually increasing doses of bretylium tosylate to 600 mg. t.i.d., and the addition of reserpine 1·5 mg. daily, the blood-pressure readings were 260/160 supine and 190/130 erect. He was vomiting after each dose of bretylium tosylate. The blood-urea was 180 mg. per 100 ml. He was readmitted, and the vomiting ceased when bretylium tosylate was discontinued. The outpatient blood-pressure readings on guanethidine are now 230/130 supine and 150/90 erect. He is taking 70 mg. guanethidine once a day and feels considerably better; but the blood-urea is 228 mg. He continues with reserpine.

Case 2.—Man, aged 53, with malignant hypertension; blood-pressure 240/145 mm. Hg, papilloedema, and blood-urea 43 mg. per 100 ml. He was started on bretylium tosylate last September and was discharged from hospital with an erect blood-pressure of 145/95, taking 300 mg. bretylium tosylate t.i.d., When he was seen two weeks later in the outpatient clinic the blood-pressure was 240/130, only dropping to 200/130 on standing. His headaches had recurred. Over the next few weeks the dose of bretylium tosylate was gradually increased and chlorothiazide started. Eventually a standing blood-pressure of 180/110 was achieved with 500 mg. bretylium tosylate t.i.d. By this time however, intolerable parotid pain had developed on which propantheline bromide had no effect. It was not possible to increase the dose of bretylium tosylate further; indeed it eventually had to be discontinued.

Case 3.—Man, aged 55, with severe hypertension; blood-pressure 240/130 mm. Hg and blood-urea 38 mg. per 100 ml. Because of poor control with trimethidinium, he was changed to bretylium tosylate last October. The dose was increased from 200 mg. t.i.d. to 600 mg. t.i.d. over a period of six weeks, and chlorothiazide and reserpine were added. Although the blood-pressure was not controlled and was 220/140 recumbent and 210/130 standing, it was thought unwise to increase the dose of bretylium tosylate further because he developed hypotensive symptoms on exertion. These were especially severe on climbing stairs and he became increasingly deaf as he reached the top of the staircase, and had to sit or lie down because of dizziness.

Case 4.—Man, aged 52, with malignant hypertension, blood-pressure 250/140 mm. Hg and blood-urea 50 mg. per 100 ml. When he was discharged from hospital last September his blood-pressure dropped from 200/120 mm. Hg to 150/100 mm. Hg on standing, on a dose of 400 mg. bretylium tosylate t.i.d. At his first outpatient attendance in October, the blood-pressure was 250/125, dropping to 230/120 on standing. The dose of bretylium tosylate was increased to 600 mg. t.i.d. and chlorothiazide was added. In March the blood-pressure was 240/130 dropping to 200/120 on standing, and he has since been changed to guanethidine with good effect.

These four cases were classified as responding poorly to treatment with bretylium tosylate.

Tolerance

Important differences were immediately noted between the two drugs under trial. Patients who had been discharged from hospital on bretylium tosylate, showing a good response to the dose given at that time, were almost always found to have uncontrolled hypertension when they made their first outpatient attendance. This necessitated increasing the dose and the patient had to come to the clinic at very short intervals. Usually, when we reached a dose of 1800 mg. daily, we did not increase it further but tried the addition of reserpine and chlorothiazide. If, after this, the blood-pressure remained uncontrolled, it was our habit to change to another form of treatment. As can be seen in table III, of the 25 patients who started bretylium tosylate in hospital only 5 were judged to be well controlled. This was a great disappointment after the initial good response in 22 of them.

In this respect patients with nitrogen retention seemed to behave in the same way as those with good renal function. Tolerance developed as rapidly in 9 patients with blood-urea levels above 40 mg. per 100 ml. as it did in those with normal values.

The attempt at outpatient control proved time-consuming and difficult, and many patients found the continual changing of dose troublesome, and the multiplicity of tablets when reserpine, chlorothiazide, and potassium were added to bretylium tosylate a further disadvantage.

In contrast to this, it was unusual for patients on guanethidine to require more than minor adjustments in dosage in the outpatient clinic, and about half of them needed no change of any sort from the regime started in hospital. Dosage has ranged from 5 mg. to 80 mg. daily, with the majority requiring about 40 mg. Very few required reserpine or chlorothiazide, and the patients were all glad to take one dose of the drug each day. In the patients on guanethidine, control of the blood-pressure was similar at various times of day, confirming our inpatient observations of its smooth even action.

Side-effects

With bretylium tosylate nasal stuffiness seems to be the most common but least troublesome side-effect. Exertional

dyspnœa has been seen frequently, and in several cases which otherwise seemed to be responding favourably it has been so prominent that treatment had to be stopped or the dose reduced. This effect has been attributed to exertional hypotension (Turner and Lowther 1960, Lowe and Rosenheim 1960). Severe parotid pain has been seen in 2 cases. Diarrhœa, which was common, was usually controlled with propantheline bromide.

Muscular weakness was sometimes seen in patients on bretylium tosylate. In one patient it was associated with abnormal electromyographic patterns, and was so severe that treatment had to be discontinued. On withdrawal of the drug the electromyograms became normal, and they remained so after good control of the hypertension had been achieved with guanethidine.

With guanethidine, our experience so far has been that diarrhœa is the most troublesome feature, but again it is usually controlled with propantheline bromide. Several cases have had mild exertional dyspnœa, but this has not been severe enough to necessitate lowering the dose or withdrawal of the drug. Only 1 patient had parotid pain, and this was mild.

We have encountered mental changes with both drugs:

One of our first patients treated with bretylium tosylate was a man of 51 with a blood-pressure of 210/140 mm. Hg, a grade-IV retinopathy, albuminuria, and blood-urea of 46 mg. per 100 ml. He proved refractory to treatment until the dose of bretylium tosylate was increased to 1500 mg. t.i.d. This significantly reduced his standing blood-pressure, but after three days on this dose he developed visual and auditory hallucinations and became disorientated. On withdrawal of the drug, his mental state returned to normal, and it remained so even when the blood-pressure was reduced to similar levels with pempidine. We have not used such large doses of bretylium tosylate subsequently.

In another patient a West Indian aged 41 with a blood-pressure of 290/155 mm. Hg, blood-urea 26 mg. per 100 ml., positive Wassermann reaction, and aortic incompetence, a paranoid psychosis developed after he had had guanethidine 25 mg. daily for ten days. His mental state returned to normal on stopping treatment but relapsed when it was restarted. Reduction of his blood-pressure to a similar level with pentolinium did not induce similar mental changes. His cerebrospinal fluid showed no abnormality, but syphilitic infection may have played some part in the mental changes for when he was last seen in the outpatient clinic he was again beginning to have some auditory hallucinations. He was given antisyphilitic treatment whilst in hospital, and, according to his wife, had been normal mentally before this. In these circumstances it is difficult to incriminate guanethidine with certainty, but in table III he has been shown as the 1 poor response to inpatient treatment. As alternative treatment was started in this case, only 16 patients on guanethidine were seen in the outpatient clinic.

Subcutaneous Bretylium Tosylate

A few patients who had become refractory to oral treatment were given bretylium tosylate subcutaneously, but the results were not good. This attempt was prompted by an earlier experience:

A woman with severe malignant hypertension and advanced renal failure was admitted as an emergency with blindness due to hypertensive retinal œdema. After several days' treatment with subcutaneous bretylium tosylate in a dosage of 50 mg. six-hourly, the hypertension was controlled satisfactorily, the retinal œdema had subsided, and useful vision had returned.

However, for the short-term rapid control of severe hypertension, subcutaneous bretylium tosylate appears to offer no particular advantage over subcutaneous pentolinium.

Conclusions

The advent of adrenergic-blocking agents is a great advance in the treatment of hypertension (Boura et al. 1959, Dollery et al. 1960). Life need no longer be made a misery by the parasympathetic effects of the ganglion-blocking agents.

Though our experience is limited, we have little doubt that guanethidine is at present the drug of choice. Its action is apparently steady; tolerance does not develop; and outpatient care of cases is relatively easy.

If our present experience is confirmed, and if our survival-rates are as good as those with pentolinium, guanethidine or some similar drug should almost entirely replace the older ganglion-blocking agents.

Summary

Of 44 patients with severe hypertension, 27 were treated with bretylium tosylate and 17 with guanethidine.

Bretylium tosylate was effective for short periods in the ward; but for long-term control it was not satisfactory, because of its transient action, the rapid development of tolerance, and the need to supplement it with chlorothiazide and other agents.

Guanethidine was much more satisfactory in outpatient control. A single daily dose was adequate, and there was only 1 outpatient failure in 16 patients, in contrast to 16 failures in 25 patients treated with bretylium tosylate.

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THE CIRCULATORY EFFECTS OF BRETYLIUM TOSYLATE AND GUANETHIDINE

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SINCE the introduction last year of bretylium (Boura et al. 1959) and guanethidine (Page and Dustan 1959), these powerful hypotensive drugs have been employed increasingly in clinical practice, and knowledge of their circulatory effects in man has become an urgent necessity. In this preliminary paper we outline their hæmodynamic effects and report that bretylium has a remarkable effect on the human pulmonary circulation.

Our studies in hypertensive patients were a preliminary to the proposed treatment of these patients with bretylium or guanethidine by mouth. The studies of patients with mitral stenosis, which were made during routine cardiac catheterisation prior to decision concerning mitral valvotomy, were initiated in view of the widely expressed hope that bretylium may have a favourable effect on pulmonary arterial hypertension.

Methods

The effect of bretylium was studied in 13 patients with uncomplicated hypertension, in 22 patients with rheumatic mitral-valve disease (predominantly stenosis), and in 6 normal subjects. The effect of guanethidine was also studied in 5 patients with uncomplicated hypertension.

All patients were studied in the supine position by cardiac catheterisation. Cardiac output was determined by the Fick method, and aortic and pulmonary arterial and wedge pressures were recorded at the same time by means of capacitance or strain-gauge manometers. Observations were made at rest, during six minutes' light exercise (oxygen uptake range 234–445 ml. per min. per sq. m.), during six minutes' moderate exercise (oxygen uptake range 475–664 ml. per min. per sq. m.), and again during the sixteenth to nineteenth minutes after cessation of exercise. The light and moderate exercises were continuous and were carried out on a constant-speed variable-load type of ergometer. Bretylium was then injected intravenously in a dose which ranged from 90 to 600 mg. (0·6–9·0 kg. body-weight) of the base. In the 5 patients in whom guanethidine was used, the drug was injected intravenously in a dose which ranged from 20 to 40 mg. (0·25–0·70 mg. per kg.). After forty-five to ninety minutes, when the resting blood-pressure had stabilised, these studies were repeated in exactly the same manner. Almost similar oxygen uptakes were achieved during comparable periods of exercise before and after the drug. The patients with chronic rheumatic heart-disease only performed six minutes' light exercise (oxygen uptake range 195–514 ml. per min. per sq. m.).

Results: Bretylium

ACUTE EFFECTS OF INTRAVENOUS INJECTION

With any but very slow rates of injection of the drug, there was pronounced facial and conjunctival flushing with a transient sensation of skin warmth in twenty to thirty seconds. The next commonest symptom was nausea, particularly with rapid injections of the drug, and 3 of the hypertensive patients experienced diplopia on upward gaze, a hitherto undescribed side-effect. This diplopia lasted only a few minutes, during which no objective ocular signs could be demonstrated. The rapid fall in blood-pressure, which occurred twenty to thirty seconds after an injection of the drug, lasted only five to fifteen seconds and was associated with a reduction in pulse pressure. In all but 3 of the hypertensive patients this immediate fall in arterial pressure was followed by a period of moderate increase in the blood-pressure to above pre-injection levels. This "hypertensive" reaction lasted from ten minutes to two hours. It was also observed in all the normal subjects but not in any patient with moderate or severe chronic rheumatic heart-disease. A separate investigation has shown that there is a more prolonged response to intravenous noradrenaline (dose range 4–8 μg. in 5 sec.) during this hypertensive phase in normal subjects. The patients with rheumatic heart-disease showed a consistent fall of systemic blood-pressure with far smaller ($^1/_8$–$^1/_4$) doses of bretylium than those given to the normal and hypertensive subjects.

The pulmonary arterial pressure increased in all normal subjects and all but 1 of the hypertensive patients twenty to thirty seconds after the intravenous injection of the drug. The increase in pulmonary arterial pressure was maintained throughout the period of the remainder of the observations (up to two hours) and was unaccompanied by changes in pulmonary wedge pressure. The dose of bretylium administered, stated as base, ranged from 120 to 180 mg. in normal subjects, from 90 to 600 mg. in hypertensive patients, and from 15 to 60 mg. in patients with rheumatic heart-disease.

RESPIRATORY RATE, VENTILATION, TOTAL BODY OXYGEN UPTAKE, AND ARTERIAL BLOOD OXYGEN SATURATION

The resting respiratory rate was largely unchanged by injection of the drug in all three groups of patients. The resting ventilation was increased slightly in the normal and hypertensive subjects (mean increase: normal subjects 1·09 litres. per min. per sq. m., hypertensive patients 0·86 litre per min. per sq. m., but not in patients with rheumatic heart-disease.

The total body oxygen uptake at rest was consistently increased in the normal and hypertensive subjects (mean increase: normal subjects 20 ml. per min. per sq. m., hypertensive patients 14 ml. per min. per sq. m.). There was no consistent change in the resting oxygen uptake of patients with chronic rheumatic heart-disease who were given much smaller doses of the drug. The arterial-blood oxygen saturation, although unaltered by the drug at rest, was slightly but consistently lower during exercise than before its administration in all normal and hypertensive subjects.

CARDIAC OUTPUT AND HEART-RATE

The resting cardiac output was significantly increased in all normal subjects and in all hypertensive patients (see figure). (Mean increase: normal subjects 0·65 litre per min. per sq. m., hypertensive patients 0·61 litre per min. per sq. m.)

As the cardiac output during recovery from the first exercise study was in many instances slightly lower than the initial resting cardiac output, a control series of cardiac-output and oxygen-uptake observations was carried out, without administration of bretylium after the first period of exercise; and in no instance did the oxygen uptake or cardiac output increase over the control period.

In the normal and hypertensive subjects the cardiac-output response to exercise, which was initially normal in all instances, was unaltered by the bretylium. There was one exception to this; a hypertensive patient who received the largest dose of the drug in the series (9 mg. per kg.) in whom the normal exercising cardiac-output response was impaired by the drug.

In the patients with rheumatic heart-disease, many of whom had low resting cardiac outputs, there was not the same consistent behaviour (see figure). All but 5 of the 22 patients showed a slight rise in resting cardiac output (mean increase 0·13 litre per min. per sq. m.) which was unchanged or slightly reduced in the remainder. The cardiac output response to exercise, which was impaired in many instances, remained unchanged.

Another interesting feature was that bretylium appeared to cause no important change in heart-rate, either at rest or during exercise, in any of these groups of subjects.

SYSTEMIC BLOOD-PRESSURE AND VASCULAR RESISTANCE

After administration of bretylium the resting blood-pressure was little changed in the normal subjects. In the hypertensive patients it was slightly reduced in 6 (mean fall 12 mm. Hg), unchanged or slightly higher in 4, and considerably reduced (mean fall 31 mm. Hg) in the remaining 3.

During moderate supine leg exercise after bretylium, the normal and hypertensive subjects showed, instead of the usual rise, which is often marked in hypertensive subjects, a reduction of arterial blood-pressure which in some of them was considerable. The mean reduction in exercising mean aortic pressure in the normal subjects was 10 mm. Hg and in the hypertensive patients 20 mm. Hg. In 2 of the hypertensive patients the fall in the exercising blood-pressure was 50 and 54 mm. Hg. In those subjects to whom doses of less than 2·5 mg. per kg. had been given, although no fall occurred, the rise of exercising blood-pressure noted in the control period was largely abolished. Although the behaviour during light exercise was more variable, 2 of the 6 normal subjects and 6 of the 13 hypertensive patients showed a small fall of blood-pressure. In a number of these there was a further marked fall of blood-pressure immediately after the cessation of moderate exercise, which recovered slowly during the next ten to fifteen minutes but in a few remained appreciably below the levels before exercise.

The patients with rheumatic heart-disease showed a consistent and often marked reduction of mean blood-pressure at rest (mean fall 18 mm. Hg, range 5–33 mm.) after bretylium. During light exercise the blood-pressure changes were inconsistent; 7 of the 22 patients showed small reductions in mean arterial pressure (mean reduction 7 mm. Hg, range 2–13 mm.)

and in the remainder the increase in blood-pressure observed during exercise in the control period was considerably reduced.

When these changes were related to blood-flow it was apparent that bretylium causes either no change or a small decrease of systemic vascular resistance at rest in supine normal subjects and hypertensive patients, but that the systemic resistance falls abruptly on moderate exertion.

In the patients with rheumatic heart-disease, in many of whom the systemic vascular resistance was of the order of that observed in patients with severe hypertension, the administration of much smaller doses of bretylium invariably caused a significant reduction of systemic resistance particularly at rest, and a slight further reduction during light exercise.

CHANGES IN REGIONAL BLOOD-FLOW

The study of changes in regional blood-flow by observation of changes in regional arteriovenous-blood oxygen-content difference (A-V difference) has been discussed fully elsewhere (Donald 1959). These changes can also be employed to give estimates of exercising leg blood-flow (Donald et al. 1957). The assumption is made that there is no important change of regional oxygen uptake during short periods of supine leg exercise except in the exercising muscles; thus the changes in regional blood-flow in non-exercising areas are inversely proportional to changes in regional A-V difference.

Normal Subjects and Hypertensive Patients

The femoral A-V difference increases greatly during leg exercise. In 6 hypertensive patients, after the administration of bretylium, both the resting and exercising A-V differences were similar to the study before the drug. As the exercising oxygen uptake was similar in the two studies in each subject, it is inferred that there was no important change in exercising leg blood-flow.

The cerebral A-V oxygen-content difference was largely unchanged in 4 hypertensive patients during exercise, both before and after the administration of bretylium.

In both normal and hypertensive subjects moderate leg exercise in the supine position caused a slight to moderate increase of the splanchnic A-V difference. After the administration of bretylium the increase of the splanchnic A-V difference during exercise was considerably greater. (Mean percentage increase in splanchnic A-V difference during moderate exercise before and after bretylium: 3 normal subjects, 21% before, 101% after; 4 hypertensive patients, 26% before, 43% after).

The renal A-V oxygen content difference was studied in 3 hypertensive subjects. After the administration of bretylium there was a considerable increase in the resting renal A-V difference (mean increase 37%, range 22–48% of the control value). The increase of renal A-V difference on moderate supine leg exercise was largely unchanged by bretylium (increases of 67 and 55% before and after respectively)

The effect of exercise on the axillary A-V difference after the administration of bretylium was quite different from that in the regions so far described. Before bretylium the axillary A-V difference in 4 normal and 6 hypertensive subjects increased during exercise. In separate studies of muscle (deep forearm) and skin (superficial hand) A-V differences in normal and hypertensive subjects before bretylium it was found that both skin and muscle A-V differences increased during exercise. The muscle A-V difference remained increased throughout and the skin A-V difference tended to lessen as exercise continued.

After the administration of bretylium the increase of total arm A-V difference during exercise was largely abolished and in some instances there was a diminution of arm A-V difference in late exercise. The effect of bretylium on the behaviour of the skin A-V difference during leg exercise was inconsistent but it tended to lessen the increase of skin A-V difference. The consistent increase of forearm muscle A-V difference during leg exercise was no longer seen after bretylium and in some instances exercise now caused a notable decrease of muscle A-V difference.

Rheumatic Heart-disease

Increased regional A-V differences, particularly in the arm and splanchnic and renal circulations, are found even at rest in patients with low cardiac outputs. It has already been reported that these patients show similar but greater adaptations of regional blood-flow to exercise than normal subjects (Donald 1959). The changes in the behaviour of the regional A-V differences during light exercise before and after much smaller doses of bretylium (15–60 mg.) were similar to those during moderate exercise in normal and hypertensive subjects. The cerebral A-V blood oxygen content difference remained essentially unchanged in 4 patients during exercise before and after the drug. The femoral (exercising legs) A-V difference was also unaltered by the drug at the same level of light exercise in 2 patients. The mean percentage increase of splanchnic A-V difference during light exercise in 6 patients before and after bretylium was 30% and 40% respectively. The response of the renal A-V difference in 4 patients to the small doses of bretylium used was slightly different to that in the hypertensive subjects. Although the resting renal A-V difference was significantly increased by bretylium in only 1 of these patients, the mean percentage increase of the renal A-V difference on light exercise was 14% before and 58% after bretylium.

RENAL FUNCTION (in collaboration with Dr. A. DOIG)

The effect of bretylium on renal blood-flow and glomerular filtration-rate (measured by *p*-aminohippurate (P.A.H.) and inulin clearances) was determined in 4 normal and 2 hypertensive subjects. The subjects were undergoing a water diuresis and remained at rest in the supine position. Reductions in mean arterial pressure of 20 to 65 mm. Hg occurred after the intravenous administration of 60–90 mg. of bretylium but the pressure did not fall below 70 mm. Hg in any instance. The effective renal blood-flow fell to 42–83% (mean fall 58%) and the glomerular filtration-rate fell to 40–70% (mean fall 61%) of the control values. These values rose gradually and reached control levels within ninety minutes of the drug's administration. There was no associated recovery of mean arterial pressure. The extraction ratio of P.A.H. was measured in 3 of the normal subjects by catheterisation of the right renal vein. In 1 subject there was no alteration in P.A.H. extraction, but in the other 2 a slight reduction was observed, the values before bretylium being 0·89 and 0·87 and after bretylium 0·81 and 0·72 respectively. A marked reduction in urine flow to 3–18% (mean 9%) of control values occurred in all 6 subjects following administration of the drug, and this antidiuresis continued after the renal blood-flow and glomerular filtration-rate had returned to control levels. The antidiuresis was associated with a reduction in both osmolal and free-water clearances of 52–85% (mean 71%) and 94–107% (mean 103%) of control values respectively and an associated rise in urine osmolality. The renal response to bretylium in the 2 hypertensive patients did not differ from that observed in the normotensive subjects.

PULMONARY VASCULAR PRESSURES AND RESISTANCE

Normal and Hypertensive Subjects

Initially the pulmonary wedge and arterial pressures were all within normal limits. The pulmonary vascular resistance was also normal except in three hypertensive patients in whom it was slightly or moderately raised. After the intravenous injection of the drug, there was little or no change in the resting pulmonary wedge pressure but a definite and sustained rise in the resting pulmonary arterial mean pressure in all normal subjects and all but 1 of the hypertensive patients. Although some of this increase in the pulmonary arterial pressure was due to the small increase in the resting cardiac output (vide supra) the major factor responsible was a considerable increase in the mean pulmonary vascular resistance (see figure). This increase persisted at all levels of exercise.

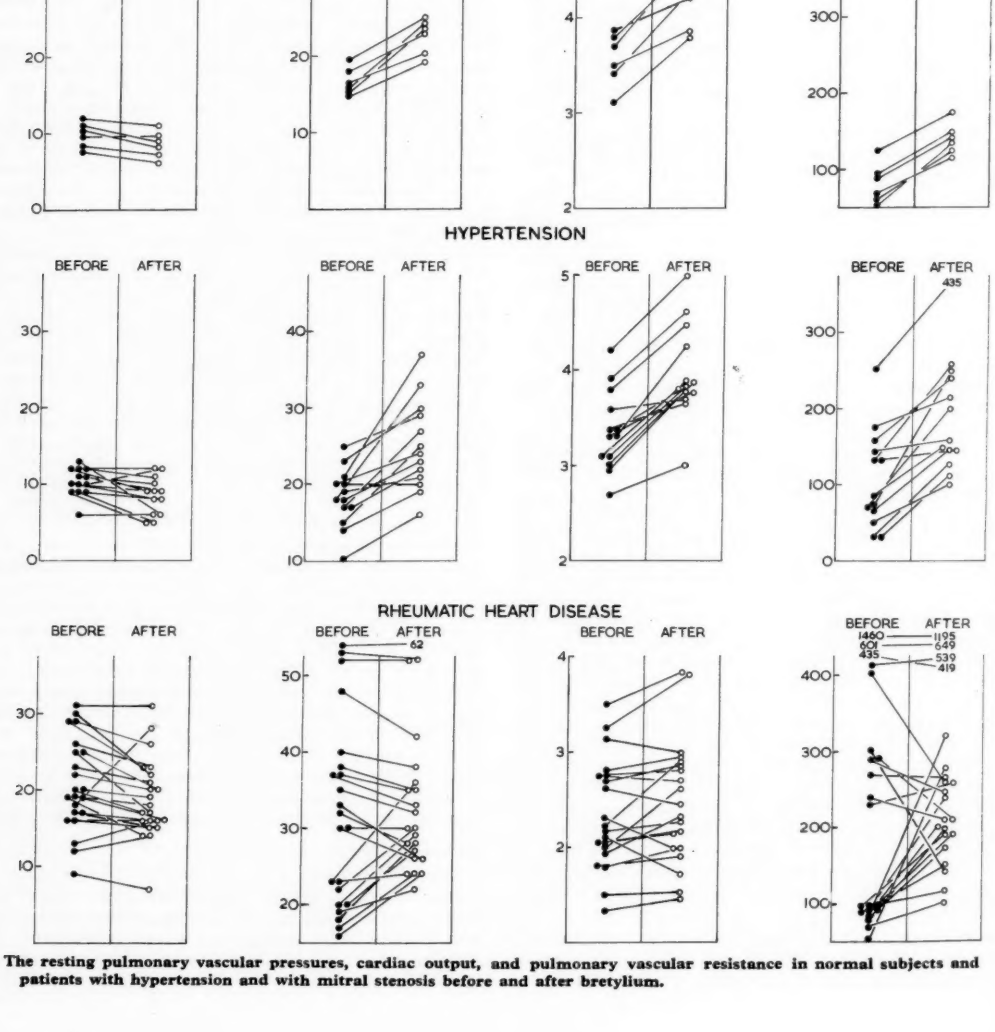
Rheumatic Heart-disease

The problem was investigated further in patients with chronic rheumatic heart-disease in whom two distinct groups were discernible (see figure). In those patients with a normal resting pulmonary vascular resistance, irrespective of the absolute levels of pulmonary wedge and arterial pressures, injection of bretylium was followed by a rise in the resting

pulmonary vascular resistance of the same order as that observed in normal and hypertensive subjects and likewise unaccompanied by any but small changes in pulmonary wedge pressure or cardiac output. However, in the 11 patients in whom the pulmonary vascular resistance was initially raised, intravenous injection of bretylium resulted in no change in 3, an increase in 2, and a fall in the pulmonary vascular resistance in 6. The changes produced by bretylium in the resting pulmonary vascular resistance of patients with chronic rheumatic heart-disease persisted during exercise.

Oral Bretylium in Hypertensive Patients

In view of these acute changes in the pulmonary vascular resistance following the intravenous administration of the drug, 3 hypertensive patients who had been treated with daily oral bretylium for more than six months were studied. These patients, aged 37, 39, and 43 years, had had no symptoms or signs of cardiac or respiratory disease or insufficiency at any time. They still showed satisfactory postural effects on the blood-pressure at the time of study, which was carried out two hours after the routine midday oral dose of the drug. A similar hæmodynamic study to that already described was carried out. At rest the cardiac outputs were 3·98, 2·81, and 4·10 litres per min. per sq. m., the mean pulmonary arterial pressures 29, 26, and 22 mm. Hg, and the wedge pressures 9, 9, and 12 mm. Hg in the respective patients. During exercise (oxygen uptakes 396, 665, and 398 ml. per min. per sq. m.) the cardiac-output response was normal in all 3, but the pulmonary arterial pressures rose to 46, 46, and 44 mm. Hg respectively. The exercising pulmonary wedge pressure remained within normal limits in the first 2 patients but rose to 23 mm. Hg in the 3rd. The calculated pulmonary vascular resistance in the first 2 patients was considerably elevated at rest (220 and 255 dyne sec. cm.$^{-5}$; upper normal value 140 dyne sec. cm.$^{-5}$) and the increase persisted during exercise.



The resting pulmonary vascular pressures, cardiac output, and pulmonary vascular resistance in normal subjects and patients with hypertension and with mitral stenosis before and after bretylium.

Results: Guanethidine

Identical studies, as outlined in Methods, have been carried out with this drug on 5 hypertensive subjects. Guanethidine in intravenous doses of 20–40 mg. caused a fall in the arterial blood-pressure within a few minutes without a " hypertensive " phase. No nausea or flushing or any other immediate side-effect was encountered. In this limited study the fall in blood-pressure in the supine position, although of moderate degree (mean fall 13 mm. Hg), was more consistent. The increase in arterial blood-pressure observed in these patients during exercise was diminished after guanethidine in 4 patients; there was a fall of 10 mm. Hg in the exercising blood-pressure of the remaining patient.

After guanethidine was given the pulmonary ventilation was increased (mean increase: 0·86 litre per min. per sq. m.) in all and the oxygen uptake in 3 (mean increase: 24 ml. per min. per sq. m.) of the 5 subjects. There was no consistent change in resting cardiac output, and the response of the cardiac output to exercise was also unchanged by this drug. The mean resting pulmonary wedge and pulmonary arterial pressures were relatively unchanged, but the calculated pulmonary vascular resistance showed a slight decrease, which was maintained during exercise in all subjects.

In view of the important findings in the arm after the administration of bretylium, the A–V difference studies were concentrated on this region. The increase of total arm A–V difference during leg exercise was reduced in all cases but 1 after guanethidine. The initial increase of skin A–V difference on exercise was largely abolished, although the later decrease of A–V difference, due presumably to skin vasodilatation, was still evident. However, there was still a considerable increase of arm A–V difference in all cases during moderate exercise despite the fact that there was now a constant or narrowing skin A–V difference. This suggested that the non-exercising muscle A–V difference increase on exercise was still considerable and, in 1 subject, in whom satisfactory deep forearm muscle venous samples were obtained, this was confirmed.

Discussion

BRETYLIUM

The small but significant rise of oxygen uptake and cardiac output in normal and hypertensive subjects after the administration of bretylium is of great interest. This finding is in contrast to the effect of ganglion-blocking drugs under the same conditions where no change in oxygen uptake and a fall in cardiac output were found (Taylor and Donald, in preparation).

It is remarkable that the cardiac-output response to exercise is unaltered by the blockade of the terminal sympathetic neurones. It is to be remembered, however, that these studies are in the supine position in which the effect of " pooling " of blood is large nullified.

The fall in systemic arterial blood-pressure during exercise in patients under the influence of bretylium in the supine position is unique as compared with other anti-hypertensive agents (pentolinium, chlorothiazide, and reserpine) so far studied by us under the same conditions. There is little doubt that this fall of blood-pressure would be far greater in the vertical position in which more pooling of blood occurs. Lowe and Rosenheim (1960) have reported syncopal attacks in patients carrying out moderate or severe exertion while under the influence of bretylium and suggested that the fall in blood-pressure may have been due to a fall in the cardiac output. Under the conditions of our investigations the fall in blood-pressure on exercise was, in fact, due to a considerable decrease of peripheral vascular resistance, the cardiac output being maintained at normal levels. However, it is likely that in the vertical position the added factor of pooling of blood will cause impairment of the cardiac output, which, combined with the considerable decrease of systemic vascular resistance, would cause even more hypotension. The further and often considerable fall in blood-pressure after exertion appears to be another potential source of danger to the patient.

As judged by the behaviour of the regional A–V differences, bretylium had the following effects on regional blood-flow in normal and hypertensive subjects during exercise in the supine position. The exercising leg and cerebral blood-flow were unaltered despite the considerable fall in arterial blood-pressure. There was an increased reduction in splanchnic blood-flow during moderate exercise which may have been due solely to the fall in arterial blood-pressure (calculated reduction of splanchnic blood-flow during exercise before and after bretylium; normals 17% and 51%, hypertensives 21% and 30%, respectively).

After bretylium the mean resting renal blood-flow of the hypertensive patients, as calculated from renal A–V difference changes, was 63% (range 52–78%) of the resting control value. This is in remarkable agreement with the effective renal blood-flow values (mean 58%, range 42–83% of control values) as determined by P.A.H. clearance techniques in 4 normal and 2 hypertensive patients. The renal-function studies support clinical experience that this drug should be given with caution to patients with evidence of severe renal insufficiency. The effect of this drug on renal function appears to be very similar to those of hexamethonium (Mills and Moyer 1953, Moyer and Mills 1953). It is noteworthy that, in contrast to the splanchnic circulation, the reduction of renal blood-flow in hypertensive patients during exercise was not quite so marked after bretylium (40% and 35% reduction of control resting value before and after bretylium).

The reduced blood-pressure during exercise after bretylium in the presence of a normal exercising cardiac output, unchanged blood-flow to the legs and brain, considerably increased reduction of splanchnic blood-flow, and maintained reduction of renal blood-flow implies a big reduction of vascular resistance in the remaining important regional circulation—i.e., non-exercising muscle and/or skin.

The findings in the arm (total arm, skin, and muscle) indicate that the important cause of the fall in blood-pressure during exercise after bretylium is paralysis of the vasoconstriction in non-exercising muscle and skin vessels that was found in these normal and untreated hypertensive subjects during leg exercise.

The changes in pulmonary vascular resistance in normal and hypertensive subjects after administration of bretylium were as definite as they were unexpected. Extreme caution is necessary in interpreting the significance of changes in the pulmonary vascular resistance (as calculated from mean pulmonary blood-flow and mean pressure gradient) in relation to changes in pulmonary vasomotricity. We shall not discuss this in detail here, but would emphasise that differential pressures between pulmonary arterial and wedge pressures were directly recorded. Further the blood-flow, heart-rate, and stroke volume did not alter markedly between the two studies. The occurrence of important changes in lung compliance or airway resistance, which may affect the pulmonary vascular resistance in a number of ways, is very unlikely in view of the very small differences in ventilatory volumes and respiratory rate both at rest and on exercise after the drug. Studies of the central blood volume before and after the administration of this drug have not been made. This factor, which can cause considerable alterations in pulmonary

vascular resistance, may be of importance in this context.

The finding of abnormal pulmonary vascular resistance and pulmonary arterial pressures in 2 out of 3 patients receiving oral bretylium is of clinical interest. In view of the occasional slight increase of pulmonary vascular resistance in untreated compensated hypertensive subjects, further studies are needed.

With regard to the effects of bretylium on patients with mitral stenosis, it should be recognised that the great increase of systemic vascular resistance usually found in this condition is an important adaptation to the low cardiac output, allowing maintenance of the arterial pressure and adequate blood-flow through essential organs and exercising muscle. These investigations showed that small doses of bretylium, even in the supine position, cause a considerable fall of blood-pressure at rest and a further slight fall during light exercise. The reduction of blood-flow to the skin and non-exercising muscle which took place during exercise was largely eliminated by this drug. In a few patients with considerably increased pulmonary vascular resistances, bretylium reduced the resistance, but this action was variable in occurrence and degree. Further, there was a rise of pulmonary vascular resistance where this was initially normal. In view of the effect of the drug on the important adaptation of regional vasoconstriction (particularly during exercise), and the variable response of the pulmonary circulation, administration of bretylium to patients with heart-disease appears to be contraindicated.

Further investigation of the finding that the increase of pulmonary vascular resistance caused by bretylium is no longer found in those patients with a raised pulmonary vascular resistance may contribute to our understanding of the causes of pulmonary arterial hypertension in this and other diseases of the heart.

GUANETHIDINE

The present limited findings show that, under these conditions, guanethidine does not have precisely the same hæmodynamic effects as bretylium. The consistent rise of resting cardiac output, the transient side-effects, the initial "hypertensive" phase, and the increase of pulmonary vascular resistance found after the administration of bretylium were not observed.

Preliminary studies of skin and non-exercising muscle A–V difference also suggest that the inhibition of effective vasoconstriction in non-exercising muscle found during exercise after the administration of bretylium does not occur with guanethidine, and this may well account for the lack of an important fall of blood-pressure on exercise.

Finally, we should once more point out that these studies are in the supine position. Studies in the standing position, both at rest and on exercise, are necessary to assess the added effects of the vertical posture.

Summary

The effects of intravenous bretylium and guanethidine on the cardiac output, systemic and pulmonary vascular pressures, and the regional circulations have been studied at rest and during exercise in normal subjects, hypertensive patients, and patients with mitral stenosis.

Bretylium caused a variable change in the resting arterial blood-pressure but a marked fall of blood-pressure during exercise even in the supine position. This fall in blood-pressure was associated with considerable changes in the regional circulatory adaptation to exercise, particularly the loss of effective vasoconstriction in non-exercising muscle during leg exercise.

Bretylium increased pulmonary vascular resistance in normal and hypertensive subjects, but not in patients with mitral stenosis who already had a raised pulmonary vascular resistance.

Guanethidine did not cause so large a fall in blood-pressure during exercise. Studies of arm arteriovenous oxygen differences suggest that the loss of vasoconstriction in non-exercising muscle during exercise is less than with bretylium.

Guanethidine did not appreciably change the pulmonary vascular resistance in hypertensive patients.

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A CONTACT-PLATE TECHNIQUE FOR DETERMINING BACTERIAL CONTAMINATION OF FABRICS

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MUCH has been written on hospital textiles as reservoirs of infectious organisms, particularly hæmolytic streptococci and *Staphylococcus aureus*. But the techniques for determining the degree of contamination of such textiles have not been as thoroughly investigated as one might have expected. The simplest and most convenient method at present used in England and Australia is the sweep-plate technique devised by Blowers and Wallace (1955) with the advice of R. E. O. Williams. Previously Thomas and Van den Ende (1941) described an apparatus for sampling hospital bedclothes, but their method was too cumbersome to be generally accepted. In 1946 Puck et al. described a percussion technique which permitted a semiquantitative estimate of organisms capable of being dislodged from the fabric under test.

Apart from these three reports, and passing mention of various methods of agitation over exposed agar plates, the problem of devising a convenient and reproducible sampling technique has not been seriously studied. In our own work on cross-infection we have depended largely on the contact-plate technique we shall now describe. Walter informs us that he and his colleagues have used an impingement technique which is similar in principle.

Materials and Methods

The method is based on the replica plating technique described by Lederberg and Lederberg (1952). An

aluminium disc, 2 mm. thick, 8·5 cm. in diameter, is mounted on a wooden handle about 9 cm. long. The textile to be sampled is stretched over the disc and brought into firm contact with an agar medium dispensed in a 9 cm. petri dish (fig. 1). This constitutes a single contact plate; but, as will be seen later, a triple contact plate is recommended, particularly when staphylococci are sought. The triple contact plate is prepared by making three contacts at different sites on the textile without changing the plate. No sterilisation of the metal disc is required.

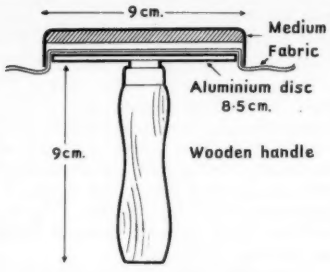

Fig. 1—Contact-plate technique.

Sweep-plate technique.—This was performed as described by Blowers and Wallace (1955).

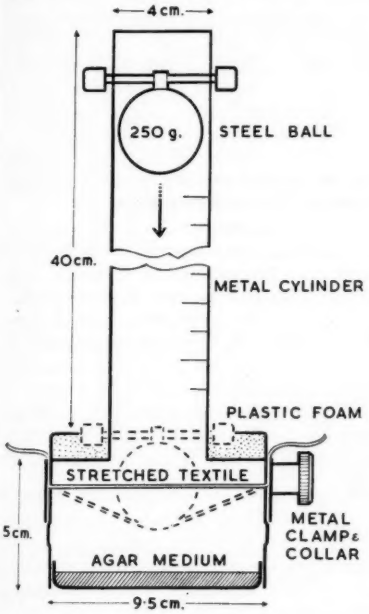

Fig. 2—Percussion-plate technique.

Percussion-plate technique.—The method of Puck et al. was modified by constructing the all-metal instrument illustrated in fig. 2. The fabric is stretched and clamped 5 cm. above an exposed agar plate in a confined space and then struck by a steel ball weighing 250 g. The height of fall and number of times the ball is allowed to percuss the material may be varied, but the results we report are calculated on the number of bacteria liberated from the fabric diaphragm after five drops at 35 cm. A settling-time of half to one minute was chosen after it had been shown that the bacterial counts did not increase with longer settling-times.

Media.—Two types of agar media used in this study were 6% blood-agar and papain-digest agar containing 8% sodium chloride. Incubation of cultures at 37°C for forty-eight hours was standard.

Textiles.—The blankets were normal hospital blankets consisting of 70% wool and 30% cotton fibre. Some were oiled by immersion in an emulsion added to the final rinse and then hydro-extracted. The oil content of these blankets was 4–5%. Counterpanes were cotton and laundered in the usual way.

Results

Sampling of Blankets

The results of an experiment, typical of many, are shown in table I. In this, three used blankets were sampled in situ by sweep-plate and contact-plate (triple contact) methods and five samples were taken from each blanket using salt-agar medium. The results (table I) show no significant difference in the counts with the different methods. It is, of course, not possible to equate accurately the surface area sampled in each method, and the interpretation of the results will be discussed later.

One important disadvantage of the sweep-plate technique is shown in fig. 3, in which typical plates are shown following the sampling of the same blanket surface by the three methods. It will be seen that, although the counts are almost the same with the sweep-plate and contact-plate techniques, the distribution of colonies in the sweep plate is mainly around the periphery of the medium, whereas with the contact plate an even scatter of colonies is always obtained. This is an important technical point when heavily contaminated materials are examined. It is also worth noting that the percussion plate gives higher counts than either contact or sweep plates, and this finding is usual with all normal blankets.

TABLE I—SAMPLING OF WARD BLANKETS BY CONTACT AND SWEEP PLATE METHODS

Medium: 8% sodium-chloride agar (see text)

Method	Blanket counts		
	No. 1 Average 5 samples	No. 2 Average 5 samples	No. 3 Average 5 samples
Contact-plate ..	114 (Range 93–135)	26 (Range 16–31)	16 (Range 4–27)
Sweep-plate ..	106 (Range 49–175)	25 (Range 19–37)	18 (Range 4–27)

This last difference is well shown in the next experiment, carried out in a surgical ward of ten beds. Two freshly laundered blankets on two separate beds were examined by the three methods on 6% horse blood agar after one, four, six, and ten days. At the same time two oiled blankets on another two beds were also sampled. The counts from the two sets of blankets, normal and oiled, were averaged and the results are set down in figs. 4 and 5.

Fig. 4 shows that the counts by sweep and contact techniques were not markedly different, whereas the counts following percussion were significantly greater than with either of the other methods during the first week, particularly on the first day. At the end of ten days all counts were much the same, but it should be noted that a comparable level of contamination is reached by six days.

When oiled blankets were sampled (fig. 5) the counts, as might be expected, were very low for percussion and sweep

Fig. 3—Typical plates following sampling of used blanket.
(a) Percussion-plate technique (240 colonies) (b) Sweep-plate technique (62 colonies)
(c) Contact-plate technique (58 colonies)

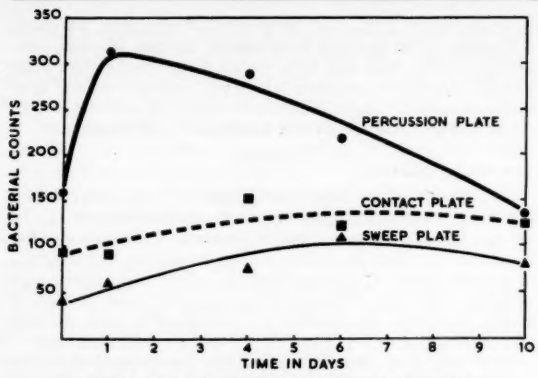

Fig. 4—Sampling of normal blanket by three methods.

plate but relatively high by the contact method. Several features of interest are reflected in these results. First, it is evident that contact plating will give a more accurate indication of the bacterial loading of oiled blankets than either of the other methods. Secondly, if used in conjunction with the percussion-plate technique, the efficiency of oiling in fixing organisms to a blanket can be assessed by noting the difference between contact and percussion-plate counts.

Sampling of Counterpanes (or Sheets)

Three counterpanes which had been in use for one day were sampled five times by sweep and contact methods using 8%

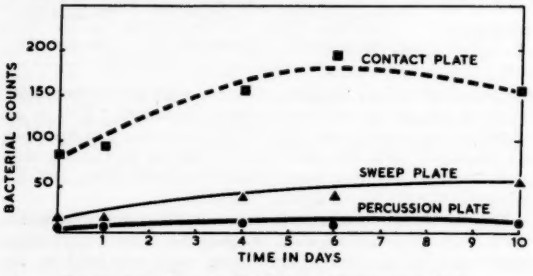

Fig. 5—Sampling of oiled blanket by three methods.

sodium-chloride agar. The results of these samplings are shown in table II. The contact-plate method yielded higher counts than the sweep-plate. This is consistent with more extensive studies which will be reported later and indicates that contact-plating is preferable to sweep-plating for isolation and enumeration of organisms on cotton sheeting.

Comparison of Sampling Methods

The counterpanes (or quilts) and top blankets of ten hospital beds were sampled in situ by three methods using horse-blood-agar and salt-agar media. The results shown in table III give a clear picture of the type of counts which might be expected in a general ward by the various methods.

It will be noted that the percussion-plate counts are always higher than the counts by other methods when woollen blankets are tested, but fall within the range of other counts when counterpanes are sampled. The most consistent results were obtained by the contact-plate method which, in this table, are

TABLE II—SAMPLING OF WARD COUNTERPANES BY CONTACT AND SWEEP-PLATE METHODS

Method	Counterpane counts		
	No. 1 Average 5 samples	No. 2 Average 5 samples	No. 3 Average 5 samples
Contact-plate ..	16 (Range 7–22)	66 (Range 17–91)	10 (Range 6–12)
Sweep-plate ..	11 (Range 6–17)	7 (Range 4–13)	3 (Range 1–6)

recorded as single and triple contact plates. The counts for the latter are approximately three times those of the former.

Variation in Sweep-plate Counts

So far it has been possible to show that samples taken from naturally contaminated normal blankets will yield approximately the same counts by sweep and contact methods. However, in all our sweep-plate samplings we were most careful to choose petri dishes with sharp ground-glass edges. If, on the other hand, petri dishes with moulded edges are used, much lower counts will be obtained. The variations in sweep-plate technique with different types of dishes is well illustrated in the following experiment.

Three types of petri dishes were used for taking five samples from a ward-soiled blanket and counterpane by sweep-plate method. It will be seen (table IV) that the counts from the blanket were consistently lower with dishes whose edges were moulded, and the same trend is apparent with the counterpanes.

TABLE III—COMPARISON OF SAMPLING WOOLLEN BLANKETS AND COUNTERPANES BY THREE METHODS

Method	Blanket counts Average 10 blankets		Counterpane counts Average 10 counterpanes	
	Blood-agar	Salt-agar	Blood-agar	Salt-agar
Percussion ..	437	413	116	115
Contact, single ..	84	54	114	78
,, triple ..	195	153	250	222
Sweep	107	185	61	108

This brings out an unsuspected variable in the sweep-plate technique which is not found in contact plating.

Discussion

The sweep-plate technique of Blowers and Wallace has much to commend it. It is simple and yields fairly consistent counts in the hands of an experienced operator. However, variable counts will be obtained with different types of petri dishes (table IV), a point not stressed by the original authors. Further, the method is unsuitable for sampling heavily contaminated materials, because of the close packing of colonies over the advancing periphery of the agar medium (fig. 3). It is equally unsatisfactory for sampling oiled fabrics (fig. 5) and cannot be conveniently

TABLE IV—VARIATION IN SWEEP-PLATE COUNTS WITH DIFFERENT TYPES OF PETRI DISHES

Type of petri dish (9 cm. diameter)	Blanket count						Counterpane count					
	Sample no. 1	2	3	4	5	Average	Sample no. 1	2	3	4	5	Average
Glass-moulded; round edge ..	3	27	45	1	8	*17*	10	5	0	0	24	*8*
Glass-ground; sharp-edge ..	49	108	88	16	41	*60*	22	14	17	12	12	*15*
Plastic-moulded sharp edge. ..	5	38	41	33	39	*31*	31	13	12	6	31	*18*
Contact-plate for comparison						41						81

used for textiles draped over metal cradles, uniforms, and masks.

The contact-plate technique has proved far more convenient and more rapid, and much more flexible in its application. For example, contact plates of upper and under surfaces of bedclothing can be made at the bedside without inconveniencing the patients. Other fabrics, such as masks, uniforms, and personal clothing, can also be easily sampled by contact plating. When three sites of a blanket are contacted with the same plate the total counts are closely similar to those obtained by the sweep plate (table I. fig. 4).

When contact and sweep-plate counts are compared for cotton textiles, the counts by contact plating are consistently higher (tables II–IV). The importance many workers

have attached to blankets may have been partly due to the relatively low counts obtained by sweep-plate method in sampling cotton textiles.

The sampling of materials treated with antibacterial agents, such as the various quaternary ammonium compounds or formalin, involves the risk of carry-over of inhibitor unless special media containing antagonists are used. Thus contact plating cannot be recommended for blankets immediately after sterilisation with formalin vapour.

It may be argued that the sweep-plate technique is a measure of bacteria capable of being dislodged from a textile on agitation, whereas contact plating is not. Up to a point this is so, but it would be misleading to extend this argument too far. For instance, when we compare the sweep-plate counts with those obtained by our modified percussion method it is immediately obvious that the sweep-plate count is not a complete measure of potential airborne organisms (fig. 4; table III). If a measure of free and fixed organisms on a fabric is desired, contact and percussion plating are better used, as seen in fig. 5. In this experiment the same oiled blankets were sampled, and counts of 3 and 91, 14 and 152, 3 and 196, and 13 and 156 were obtained for percussion and contact plating respectively, indicating the value of oiling as a method of fixing bacteria to blankets.

Contact plating, using the triple-contact count, is a simple and effective means of determining the degree and nature of the bacterial contamination of fabrics of an area greater than that of a normal petri dish. Walter and his colleagues have successfully used their similar technique in studying the spread of staphylococci in a hospital environment (Walter et al. 1958–59).

Summary

1. A method of determining the degree of bacterial contamination of all types of textiles is described.

2. This contact-plate technique is simple and rapid and can be used in wards without disturbing patients.

3. It is economical in media and gives a good distribution of colonies over the medium.

4. Unlike other methods, it is suitable for sampling all types of textiles, blankets, counterpanes, sheets, pillow-slips, personal clothing and masks.

We wish to thank the medical research fund of the University of Melbourne for financial support to one of us (S. D.) and the staff of St. Vincent's Hospital and the Royal Melbourne Hospital for permission to work in their wards.

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"... The selves we are are to a great extent the product of our social contacts. It is from society that we get the indispensable tool of language, including those systems of non-vocal gestures which are used for communication by deaf-mutes. It is from society that we get most of our interests because society provides us with a range of differentially valued activities in which we are invited to participate. It is from society that we acquire our basic moral standards; they can come from nowhere else. Thus a child brought up among the Eskimo, the Samoans, the Chinese, the English, or the Hopi Indians will have a personality appropriate to the culture in which he has been nurtured. The concept of 'human nature' has dwindled to a few basic biological needs and a large range of potentialities one selection of which is cultivated by one society, another by another. This should make us pause to reflect when the educationalists speak about 'the full development of the personality' as being the aim of education. ..."—W. J. H. SPROTT. *Human Groups.* London, 1958.

VEHICLES OF TRANSMISSION OF AIRBORNE BACTERIA IN HOSPITAL WARDS

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THOUGH much has been written about ways of controlling dust in hospital wards, there is still some doubt whether these actually reduce cross-infection. It has been shown repeatedly, for example, that oiling of blankets will reduce the number of bacteria liberated during bedmaking, but it is less clear that it will reduce ward infection.

Until quite recently it was assumed that ward dust consists mainly of wool fibres, but Pressley (1958) found that it consisted mainly of cellulose fibres, the cellulose content varying from 60% for fluff collected on floors to over 90% for airborne fibres.

His method of collecting airborne fibres was criticised by Watson (1959), but this criticism was shown to be without foundation (Pressley 1959).

Gardener and Pope (1960) using Pressley's methods, found that ward dust has a mean staphylococcal-micrococcal count of 3670 per mg. of fibre. They concluded that one way of reducing airborne ward infection would be to prevent cotton goods from shedding contaminated cellulose fibres.

Schwabacher et al. (1958) reported that airborne bacterial counts were less when cotton blankets replaced woollen ones. Lennox (1959) pointed out that the so-called woollen blankets used in this study contained only 10·4% by weight of wool. In reply, Schwabacher (1959) stated that "woollen blankets produce fluff which has proved to be a major factor in cross-infection". But her own results (1958b) are unconvincing on this point.

In an attempt to resolve the confusion about the relative importance of different textiles as sources of airborne infection, we have studied the problem from two points of view. In this paper we describe a study of the vehicles by which airborne bacteria are transmitted in hospital wards, while a later paper will report the movement of a marker organism introduced in a ward on a known textile at a specified time.

Hospital dust can be conveniently separated into two physical forms—large-fibre particles and small-fibre particles or "fibre nuclei". The former are visible to the naked eye and because of their weight do not remain airborne except by mechanical agitation. The fibre nuclei, on the other hand, may remain airborne simply through the movement of air. The object of the present study has been to assess the relative importance of these two forms of hospital dust.

Materials and Methods

The collection of bacteria and fibres was made with exposed settle-plates mounted on shelves which, in turn, were carried on four movable stands distributed throughout the ward. On each shelf at 0, 3, 6, and 9 ft. above floor level were placed a 6% blood-agar plate, an 8% salt-agar papain-digest-agar

TABLE I—AVERAGE COUNTS OBTAINED AT VARIOUS HEIGHTS ABOVE FLOOR LEVEL

Media—6% horse-blood agar (=total count); 8% sodium-chloride (=staphylococcal count)

Height above floor (ft.)	Total count		"Staphylococcal" count	
	No. of plates counted	Average count *	No. of plates counted	Average count *
0	152	51	143	24
3	152	48	146	25
6	152	47	143	26
9	152	40	140	22

* Expressed as the number of colonies settling per hour on a 9-cm. plate.

plate and a 2·5% aqueous gelatin gel containing 0·5% phenol (in dry summer weather 10% glycerin was added as a humectant). The blood-agar counts have been recorded as a "total" bacterial count; and the salt-agar count, which yields predominantly a staphylococcal-micrococcal flora, has for convenience been referred to as a "staphylococcal" count. The fibre count was performed by a gravimetric technique (see below). The times of exposure of all settle-plates for any experiment extended over a period of twenty-four hours. The fibre collection plates were not changed during the twenty-four hours but the bacteriological plates were usually changed three times during the test period. They were then incubated for forty-eight hours at 37°C.

Counting and Identification of Fibres

The fibres adhering to the tacky surface of the gelatin were recovered by melting the gel and filtering through a sintered-glass Gooch

TABLE II—STAPHYLOCOCCAL COUNTS AT DIFFERENT HEIGHTS IN THREE WARDS AT DIFFERENT TIMES OF DAY

Medium—8% sodium-chloride agar

Hospital ward	Time of sampling	"Staphylococcal" count * at			
		0 ft.	3 ft.	6 ft.	9 ft.
A. Old ward; 2nd floor; 13 ft. ceiling. Window ventilation. Blankets 70% wool, 30% cotton	Morning 9 A.M.–2 P.M.	61	54	52	50
	Afternoon 2 P.M.–5 P.M.	41	42	49	41
	Night 5 P.M.–9 A.M.	19	27	31	30
	Average whole day	40	41	44	40
B. Modern ward; 2nd floor; 10 ft. ceiling. Plenum ventilation. Blankets 70% wool, 30% cotton	Day 9 A.M.–5 P.M.	57	58	60	61
	Night 5 P.M.–9 A.M.	35	37	41	28
	Average whole day	46	47	50	45
C. Modern ward; 7th floor; 10 ft. ceiling. Window ventilation. Blankets 100% wool	Morning 9 A.M.–11 A.M.	104	68	68	46
	Afternoon 11 A.M.–5 P.M.	33	24	23	20
	Night 5 P.M.–9 A.M.	18	23	26	20
	Average whole day	52	38	39	29

* Expressed as the number of colonies settling per hour on a 9-cm. plate

crucible of porosity 3. (Certain high-quality gelatins e.g., 'Difco', will not filter and such gels must first be digested by incubation at 37°C with trypsin for one hour.) The sediment of fibres was carefully washed with a fine jet of hot water and then dehydrated with acetone. The compact ball of fibre fluff was dried in a hot-air oven at 104°C, removed with forceps, and weighed on a micro balance. After weighing, the fibres were identified by differential staining according to the technique previously described (Pressley 1958). The staining mixture was modified thus—solar scarlet RL (Sandoz) 5 g., brilliant alizanine milling blue RWL (Sandoz) 3 g., sodium sulphate hydrated 10 g., sulphuric acid concentrated 10 ml.

Ward Structure

All samples were collected in general surgical wards in two hospitals. One ward was on the second floor of the old section of a hospital in which the ceiling height was 13 ft. Another ward was in the new section of the same hospital, also on the second floor, where the ceiling height was 10 ft., and the third ward was on the seventh floor of another hospital in which ceiling height was 10 ft. The ventilation in the first and third wards was by open windows, and in the second by 'Plenum' system, but often the windows were open.

Results

Table I shows the average bacterial counts obtained at different heights above the floor in the three wards and expressed as the number of colonies collected per hour per 9 cm. plate. It will be seen that the total bacterial count was lowest at the 9 ft. level but "staphylococcal" count showed little variation with height. From a restricted number of samples taken above 9 ft., both total and "staphylococcal" counts showed a marked reduction. The trend of these results makes it clear that in wards with open-window ventilation there is no change in the airborne "staphylococcal" count in samples taken at heights up to 9 ft.

Of the hundreds of bacterial counts we shall here show only some randomly selected counts taken in the different hospitals

TABLE III—FIBRE COUNTS OBTAINED AT VARIOUS HEIGHTS ABOVE FLOOR LEVEL

Height above floor (ft.)	Fibre count * (mg.)	Composition of fibres		
		No. of fibres examined	Protein (%)	Cellulose (%)
0	0·074	12,430	20·6	79·4
3	0·018	4672	12·6	87·4
6	0·004	1426	8·8	91·2
9	0·004	1143	6·9	93·1

* Expressed as the average weight of fibres settling per 24 hours on a 9-cm plate.

at different times of the day (table II). These were remarkably constant irrespective of the height at which the samples were collected. The two wards A and B in the same hospital, although very different in construction, showed little difference in the average counts. In the other ward, C, on the seventh floor of another hospital, the average counts at the different levels were slightly lower than those for A and B. Finally, as might be expected, the night counts were always lower than the morning counts in the same ward, at all levels.

As already stated, gelatin settle-plates were exposed at the same time as the culture plates, in order to obtain an airborne-fibre count. Table III shows that at 6 and 9 ft. the weight of fibres collected after twenty-four hours' exposure was barely measurable. As expected, the fibres had a high cellulose content and this increased in samplings at increased heights.

The important features of these two sets of results is clearly defined in fig. 1. The measurable fibre content of air fell dramatically with increasing height above the floor, whereas the bacterial counts remained constant.

This spatial separation between airborne organisms on the one hand and airborne fibres on the other can be easily con-

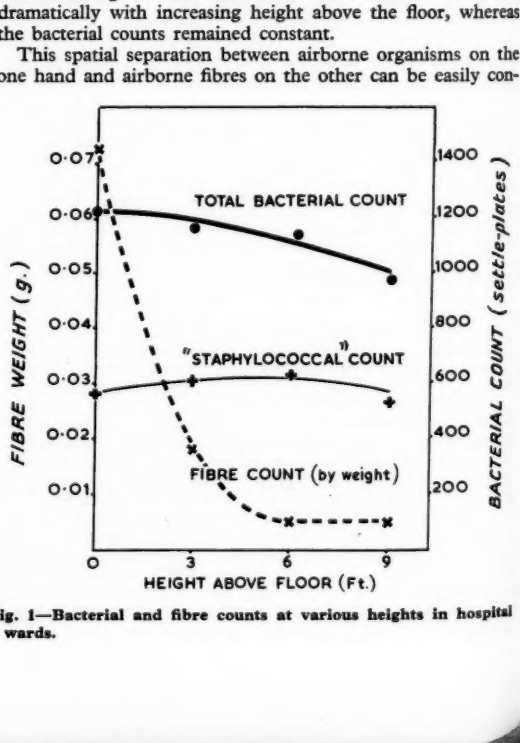

Fig. 1—Bacterial and fibre counts at various heights in hospital wards.

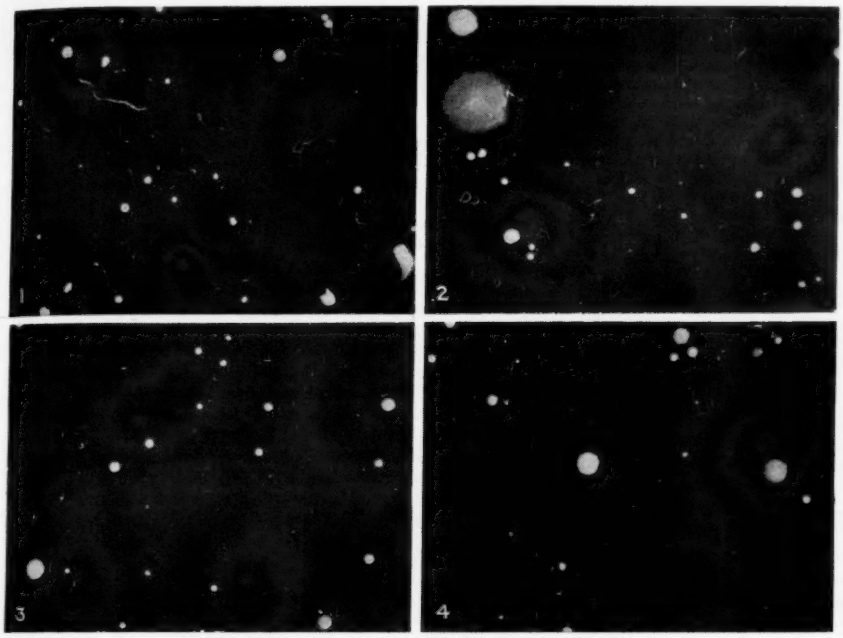

Fig. 2—Settle-plate cultures collected at various heights.

Top left: Culture at floor level. Top right: Culture 3 ft. above floor.
Bottom left: Culture 6 ft. above floor. Bottom right: Culture 9 ft. above floor.
Colony counts vary from 18 to 24. fibre counts from 5 to 27.

firmed by simpler and less arduous techniques; for example, careful inspection of culture plates will show the lack of correspondence between bacterial colonies and visible fibres on the agar surface (fig. 2).

Discussion

In three structurally different hospital wards the bacterial content of air, particularly the " staphylococcal " count on salt-agar, was similar and constant at all levels up to 9ft. above the floor (table I). Fibre counts made at the same time showed that airborne fibres were practically undetectable at heights 6 ft. above floor level (table III; fig. 1). Thus it was clear that, quantitatively, the visible and detectable fibres contributed little to the bacterial content of ward air. This finding was confirmed by the inspection of settle-plate cultures on which the spatial separation of visible fibres and bacterial colonies was readily recognised (fig. 2).

Analysis of fibres by differential staining confirmed our previous finding of the high cellulose content (table III). In the wards of one hospital, blankets consisting of 70% wool and 30% cotton were used, whereas in the second hospital the blankets were 100% wool. This made no difference to the results. Since there is little doubt that hospital dust is largely composed of cellulose, and as this fibre is lighter than wool and more easily fragmented, it might be assumed that the airborne fibre nuclei are essentially cellulose particles, arising mainly, but not exclusively, from cotton sheeting, dressings, and personal clothing. In short, it appears that airborne organisms are seldom carried on the large woollen fibres.

It now remains to discuss whether the organisms are attached to fibre nuclei or exist as free organisms or arise from droplet nuclei (Wilson and Miles 1955). On the available evidence we cannot draw too rigid a distinction between fibre nuclei and free organisms: attempts are being made to develop a technique which will distinguish the two forms. However, both are presumed to arise mainly from the same secondary reservoirs, fibre nuclei most probably from cotton textiles and free organisms from woollen as well as cotton fabrics. Droplet nuclei, on the other hand, while possessing the same dispersability as fibre nuclei, can be viewed differently from an epidemiological standpoint in that they originate by dehydration of droplets expelled during respiratory activity. Although we did not attempt experimentally to distinguish between droplet and fibre nuclei it would seem that the former play a minor part in contaminating a ward environment. This point was thoroughly investigated in an earlier study (Rubbo and Benjamin 1953), although the concept of fibre nuclei was not developed at that time. There it was shown that agitation of contaminated fabrics (handkerchiefs) produced far more airborne bacteria, presumably free or on fibre nuclei, than the most vigorous vocal activities.

The findings reported here are consistent with the concept that airborne infection in hospital wards is caused by the dispersion of pathogens travelling either as free organisms or in association with the microscopic fibre particles which we have termed fibre nuclei. The finding that airborne hospital dust is composed largely of cellulose suggests that fibre nuclei are predominantly cellulose in nature. Hence, it follows that woollen fibres and droplet nuclei quantitatively have a minor role in airborne ward contamination. Blankets (cotton or wool) constitute a danger only in so far as they liberate free organisms or fibre nuclei into the environment, and the effect of oiling procedures is to fix organism or fibre nuclei to the oiled surface. The fixation of visible woollen fibres to an oiled blanket is, as regards air hygiene, relatively unimportant.

Summary

In a study of the transmission of airborne bacteria in hospital wards the degree of air contamination was found to bear no relation to the degree of air pollution by detectable fibres.

Accordingly, it is postulated that airborne transmission of organisms takes place through the movement of free organisms or of organisms attached to microscopic fibres for which the term " fibre nuclei " is introduced. Those fibre nuclei probably consist of cellulose.

It is suggested that dust control measures, such as oiling of blankets, reduce airborne bacterial contents by fixing the free organisms or fibre nuclei to the blanket surface.

Visible woollen fibres and droplet nuclei do not seem to play a significant part in airborne contamination of wards.

We wish to thank most sincerely the nursing staffs of St. Vincent's and the Royal Melbourne Hospitals for their cooperation—in particular, Mother Dorothea Devine and Sister Mary Berchmans of St. Vincent's Hospital. Our thanks are also due to the medical research fund of the University of Melbourne, to the Hospital and Charities Commission of Victoria, and to the Commonwealth Scientific and Industrial Research Organisation, for financial assistance.

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OBSERVATIONS ON PENICILLIN "B"

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THE isolation of 6-amino-penicillanic acid in a pure form from penicillin fermentations by Batchelor et al. (1959) has permitted the synthetic development of a wide range of penicillins by the introduction of new side-chains. One of these new penicillins, the potassium salt of 6-(α-phenoxypropionamido)-penicillanic acid (penicillin "B" or 'Broxil') has been subjected to trial with encouraging results. It is given orally and has an activity similar to that of penicillin G and penicillin V. It is said to be particularly well absorbed, giving blood levels, after 1 hour, two to three times greater than those produced by similar doses of potassium penicillin V (Knudsen and Rolinson 1959). Garrod (1960) found that against penicillinase-producing strains of *Staphylococcus aureus* it was usually more active than penicillin G, with penicillin V occupying an intermediate position.

These findings have not, however, been confirmed by workers in the U.S.A. From a relatively small series of investigations McCarthy, Hirsch, and Finland (1960) concluded that penicillin B and potassium penicillin V were absorbed in essentially the same manner in normal people and that both were qualitatively similar to penicillin G in their activity on penicillinase-producing strains of *Staph. aureus*. Griffith (1960), in a cross-over trial on normal adults, found that, with equivalent dosage, potassium penicillin V gave much higher blood levels than the B form (called α-phenoxyethyl penicillin or 'Syncillin') after $^1/_4$ and $^1/_2$ hour and similar levels at 1 hour. There was considerable individual variation in the degree of absorption but the maximum levels produced by the V form were higher than those by the B form.

In view of these rather conflicting reports, we have studied the absorption, after oral administration, of both the V and B forms and also the relative activity of the G and B forms against various freshly isolated strains of *Staph. aureus*.

Methods

250 mg. of penicillin B and potassium penicillin V were given in tablet form to the same group of normal, ambulatory adults, about $2^1/_2$–$3^1/_2$ hours after breakfast—i.e., under semi-fasting conditions. There was usually an interval of several days between the different types of tablets. Samples of blood were collected 35–80 minutes later; the serum was separated without delay and tests were then carried out by the serial dilution method. The sera were kept at −25°C for further testing.

The serial dilution method was carried out by the standard technique, using 0·5 ml. volumes of a special assay medium and an inoculum of 0·02 ml. (one drop from a "fifty-dropper") of an undiluted overnight broth culture of a sensitive strain of *Staph. aureus* (T.91); this strain was used throughout the trial and, on repeated testing, always gave the same minimum inhibitory concentration with G, V, and B forms of penicillin. To obtain greater precision than is possible with the usual doubling dilution method, four series of dilutions were prepared commencing with serum dilutions of 1 in 2, 1 in 5, 1 in 7, and 1 in 9. Readings were made after 18 hours' incubation at 37°C.

In the sensitivity tests, all strains of *Staph. aureus* had been recently isolated from infective material. Standard solutions of penicillin G and B were prepared from pure salts in the special assay broth. Twofold dilutions, in 0·5 ml. volumes, were made and the inoculum was 0·02 ml. of an undiluted overnight broth culture of the strain of *Staph. aureus* under investigation. The results were read after 18 hours' incubation at 37°C.

In addition many strains were also tested against penicillin V, solutions of which were freshly prepared from a pharmaceutical preparation of the potassium salt.

Results

Blood Levels

Nineteen adult volunteers (fourteen males and five females) received 250 mg. tablets of penicillin B, usually $2^1/_2$–3 hours after breakfast, and samples of blood were collected 50–80 minutes later. Eighteen of them were later given 250 mg. tablets of potassium penicillin V under similar conditions and samples of blood were collected 40–75 minutes later. In a few instances, further samples of blood were collected.

The penicillin B tablets readily disintegrated and, unless swallowed immediately, had a very unpleasant and bitter taste; with the V tablets this effect was rather less. Otherwise the tablets were well tolerated, but one male developed an allergic reaction, with generalised urticaria, after the B tablets and consequently the V tablets were not given to him. The blood levels are expressed in μg. per ml. (1 μg. of penicillin G = 1·670 units) and the results are given in table I.

The amount absorbed by different individuals varied considerably with both forms of penicillin. With penicillin B the range was 1·08–6·72 μg. per ml. and with the V form 0·48–4·32 μg. The B form gave the higher average blood level as well as the highest individual absorption found under the conditions of the test—namely, 6·72 μg. per ml. or 11·2 units per ml. In fourteen out of eighteen volunteers, the levels with the B form were higher than those obtained with the V form.

In one subject, the levels were 4·8 μg. per ml. after 1 hour, 0·12 μg. after $3^1/_2$ hours, and after 6 hours penicillin was not detected. This agrees with the observations that penicillin B is rapidly absorbed and rapidly excreted; frequent dosage is thus essential.

Activity against Staphylococci

To determine the relative activity of penicillin G and B against freshly isolated strains of *Staph. aureus*, 105 strains (35 sensitive and 70 resistant to penicillin) were examined.

TABLE I—COMPARISON OF SERUM LEVELS OBTAINED WITH 250 MG. TABLETS OF PENICILLINS B AND V

—	Penicillin B			Penicillin V		
	Serum level (μg. per ml.)	Time range (min. after dose)	No. of subjects	Serum level (μg. per ml.)	Time range (min. after dose)	No. of subjects
Range	1·08–6·72	50–80	19	0·48–4·32	40–75	18
Overall mean ..	3·06	50–80	19	1·98	40–75	18
Mean at "peak period" ..	3·30	50–60	15	2·23	40–50	13

The sensitive strains gave consistent results with little difference between the three types of penicillin. 33 out of 35 (94%) strains gave identical readings with penicillins G and B, with a minimum inhibitory concentration of 0·03 or 0·06 μg. per ml., while the other 2 strains gave a difference of one tube, which is within the limits of experimental error for the double-dilution test. Similar results were obtained on repetition of these tests. Penicillin V also gave the same minimum inhibitory concentration in 28 out of 35 strains (80%); the remaining 7 exhibited a difference of only one tube.

A slightly greater variation was given by resistant strains of *Staph. aureus*. 55 out of 70 (79%) exhibited no significant difference but a greater-than-one-tube difference was found in fifteen after overnight incubation (table II). These differences, however, tended to disappear on further incubation of the tests at 37°C. It was also noticed that strains, giving a relatively wide difference between the G and B forms of penicillin, often gave a definite zone of inhibition around the penicillin discs in the routine sensitivity tests, but insufficient for them to be called sensitive.

The discrepancy between these results and those of Garrod seemed to be due to variations in the rate and amount of penicillinase produced by the different strains of *Staph. aureus*. We therefore decided to compare the different techniques and at the same time to carry out a series of tests with a more diluted inoculum. In our tests, 0·02 ml. of the culture was added to 0·5 ml. of medium; in the Garrod series, 0·02 ml. of culture was added to 2·5 ml. of medium; in the third series 0·02 ml. of a 1/10 dilution of the culture was added to 0·5 ml. of medium, the final inoculum dilutions being 1/26, 1/126, and 1/251.

TABLE II—ANALYSIS OF MINIMUM INHIBITORY CONCENTRATIONS OF PENICILLINS G AND B ON 70 RESISTANT STRAINS OF *Staph. aureus*

Relationship of M.I.C. of penicillins G and B	No. of strains
No difference	37
G>B(×2)	18
G>B(×4)	12
G>B(×8)	3

3 sensitive and 23 resistant strains were examined by the three different techniques. Representative results are given in table III. The sensitive strains gave the same or similar minimum inhibitory concentrations with the different techniques. Differences were, however, observed with some resistant strains, particularly those exhibiting greater resistance to the G form of penicillin than the B in the earlier tests (table II). The greater the dilution of bacterial suspension in the tests, the less became the minimum inhibitory concentrations with both penicillin B and G, and the relatively more active penicillin B appeared. These differences tended to disappear on further incubation.

The activity of the different penicillins thus appeared to depend mainly on the technique used for the sensitivity tests, particularly on the final dilution of the bacterial suspension and length of incubation of the tests.

TABLE III—MINIMUM INHIBITORY CONCENTRATION (MICROGRAMMES PER MILLILITRE) OF PENICILLINS G AND "B" WITH INOCULA OF DIFFERENT DILUTIONS

Author's technique (inoculum dilution 1/26)		Garrod's technique (inoculum dilution 1/126)		Further dilution technique (inoculum dilution 1/251)	
G	B	G	B	G	B
>512	>512	512	512	128	128
512	512	128	128	64	64
512	256	128	16	256	8
256	128	128	32	256	16
256	64	128	32	128	16
256	64	64	8	64	2
256	32	64	4	128	2
128	32	128	16	64	8
0·06	0·06	0·06	0·06	0·06	0·06
0·06	0·06	0·06	0·06	0·03	0·03

Discussion

The oral administration of penicillin to adults was unsatisfactory for a long time because of the poor and irregular absorption of penicillin G (Fairbrother and Daber 1954). The introduction of pencillin V was a major advance and this was followed by the development of potassium penicillin V, which was found almost invariably to give higher blood levels than the free acid form (Colquhoun et al. 1957). In consequence administration of penicillin by mouth is now generally accepted.

Penicillin B should prove a useful addition to the list of oral products. It is readily absorbed after oral administration and there is now much evidence to indicate that it produces higher blood levels than other oral preparations. The results in table I indicate that higher levels were obtained than with equivalent doses of potassium penicillin V. In view of the individual variation in the rate and amount of absorption, it is impossible to give an exact quantitative assessment of the two compounds without carrying out a large number of blood levels on many subjects at frequent intervals (5–10 minutes) after ingestion.

Potassium penicillin V appears to be more rapidly absorbed than penicillin B, and the peak levels are often found 30–45 minutes after ingestion (Wright and Welch 1958). In the case of penicillin B, maximum absorption is usually found at 45–60 minutes (Knudsen and Rolinsen 1959). A comparison based on readings taken at one standard time after administration, such as 1 hour, may thus give misleading results.

Nevertheless in this double cross-over trial, when samples of blood were collected at the most favourable times for the two preparations, penicillin B gave a higher average reading as well as higher maximum and minimum levels than potassium penicillin V.

It is, however, important to note that, although this preparation is usually well tolerated, an allergic reaction developed in one of the nineteen volunteers.

The suggestion that penicillin B might be used in the treatment of resistant staphylococcal infections cannot be supported. There was little difference in the results of the sensitivity tests with the G and B forms of penicillin when a heavy inoculum of the penicillinase-producing strains of *Staph. aureus* was used. There was, however, a marked difference with some strains when the inoculum was diluted; the B form tended to be more active under such conditions. This trend became greater with increasing dilutions of the bacterial suspension.

In the case of established staphylococcal infections, the lesions are likely to contain a relatively large amount of penicillinase which would rapidly inactivate any penicillin gaining access to the lesions after the usual therapeutic dosage. It is therefore much better to treat these infections with an active antibiotic, such as erythromycin, novobiocin, or even vancomycin, if the infection is severe, than to rely on the uncertain activity of penicillin.

Summary

Penicillin "B" is readily absorbed after oral administration. While there is considerable individual variation in the blood levels produced after the ingestion of 250 mg., they tended to be higher than those following the same dose of potassium penicillin V.

Penicillin B, by our technique, differed little from penicillin G in activity on penicillinase-producing strains of *Staph. aureus*. It cannot therefore be recommended

for use in the treatment of infections with resistant strains of *Staph. aureus*.

We wish to thank our colleagues for participating in the trial and Beecham Research Laboratories Ltd. for the supply of penicillin "B" or 'Broxil'.

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THYROGLOBULIN ANTIBODIES IN PATIENTS WITHOUT CLINICAL DISEASE OF THE THYROID GLAND

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WORKERS from several centres have now confirmed the observations of Roitt et al. (1956) and of Witebsky et al. (1957) that autoantibodies reacting in vitro with thyroglobulin can be found in the sera of patients with thyroid disease. It is not yet established whether or not these human antibodies are autoaggressive in vivo.

The sensitive tanned-cell hæmagglutination (Witebsky et al. 1957) and complement-fixation tests using thyrotoxic antigen (Trotter et al. 1957) detect antibodies in most cases of thyroiditis and myxœdema, but also in a significant proportion of cases of thyrotoxicosis and other thyroid disorders. Although some positive results with these techniques have been reported in patients without thyroid disease (Owen and Smart 1958, Roitt and Doniach 1958, Blizzard et al. 1959, Goudie et al. 1959), it has not been suggested that such "false" or unexpected positives are frequent except in older women who may have subclinical thyroiditis of the type reported by Goudie et al. (1959).

We report here that (using the tanned-cell hæmagglutination technique) we have found thyroglobulin antibodies in the sera of 18% of 387 mixed medical hospital patients in Adelaide, in whom there was no clinical evidence of thyroid disorder. Throughout our paper we refer to these as the non-thyroid cases.

Materials and Methods

Tanned-cell Hæmagglutination Technique

Boyden's technique (Boyden 1951) using washed sheep erythrocytes was followed with the modifications introduced by Fisher (1952) and applied to the detection of antibodies specifically reacting with human thyroglobulin with which the sheep cells were coated. An antigen-inhibition control, a diluent control, an untanned-cell control, an uncoated tanned-cell control, and known positive and negative serum controls were included in each run.

Erythrocytes.—Sheep were bled into Alsever's solution and the cells used when between three and seven days old.

Thyroglobulin was prepared by the method of Derrien et al. (1948) from human glands removed at necropsy. Preliminary chessboard titrations were performed to determine the optimum concentration of antigen; this was the minimum dose giving the highest titre.

Patient's sera were stored at −20°C. Portions were removed for each test and inactivated for thirty minutes at 56°C.

Hæmagglutination Titre

'Perspex' well-plates were used for the hæmagglutinations. The reagents having been mixed, the plates were left overnight on the bench and read the following morning. Agglutination patterns were graded from the strongest to the weakest visible with the naked eye as +++, ++, +, ±, and −. ± and − were regarded as negative. Sera were put up in doubling dilutions starting at 1/10, and no serum was tested at a greater strength than this. The end-point of a titration was taken as the last tube reading +. A "positive result" was hæmagglutination at a dilution of 1/10 or higher.

Thyroid Diseases

Blood was taken in the Royal Adelaide Hospital from patients in whom a firm diagnosis of thyroid disease had been reached by the usual clinical and laboratory methods, including measurement of the basal metabolic rate, serum protein-bound iodine, and radioactive-iodine uptake. Histological confirmation was obtained only in cases where thyroidectomy was performed.

Non-thyroid Cases

Blood was taken as a routine from all patients admitted to the wards of the medical professorial unit of the Royal Adelaide Hospital. 20 sera (3 of which gave positive results) sent by colleagues from cases of diffuse lupus erythematosus, of "diffuse collagen disease", or with abnormal serum electrophoretic patterns, in other clinical departments of the same hospital, were also included, and so there is in our material some weighting of these conditions over and above their random occurrence in the medical beds of the hospital. The whole series was obviously affected by many selecting influences, such as the special interests of consultants, and the organisation and scope of the medical services in the areas from which the hospital draws its patients, but the 387 cases were chosen before the results of the antibody tests were known.

Results

Non-thyroid Cases

The results of the tanned-cell hæmagglutination (thyroglobulin) tests in our series of 69 thyroid cases confirmed that the technique in our hands had a sensitivity comparable to that reported by other workers. Consequently, it was surprising to find that 9% of 102 blood donors and 18% of 387 hospital medical cases, chosen for their apparent freedom from thyroid disease, should give positive reactions too (table I).

We therefore reviewed all of the 68 non-thyroid cases giving positive reactions and made sure that they did not have clinical thyroid disease as ordinarily recognised. Biopsy of the thyroid glands of these patients was not justified. The diseases they had are given in table II. Positive findings were not related to recent blood-transfusion.

The 5 positive male cases in the Miscellaneous and Undiagnosed section were suffering from parkinsonism, thrombophlebitis migrans, left ventricular failure from unknown cause, pyrexia of unknown cause, and barbiturate overdosage; and the 5 females from anxiety state, fæcal impaction in a mental defective, aneurysm of the internal carotid artery, senile

TABLE I—RESULTS OF TANNED-CELL HÆMAGGLUTINATION (THYROGLOBULIN) TESTS

(The 69 thyroid cases comprised 66 females and 3 males.)

Patients	Number tested	Positives	%
Thyroid disease			
Hashimoto's thyroiditis	8	6	75
Myxœdema	20	12	60
Thyrotoxicosis	23	13	57
Euthyroid goitre	16	10	62
Carcinoma of thyroid	2	1	..
Total ..	69	42	61
Mixed medical patients without thyroid disease	387	68	18
Normal blood-donors	102	9	9

osteoporosis, and spontaneous crush fracture of the body of T8 of unknown cause.

The incidence of positives in non-thyroid cases rose with increasing age in the female (fig. 1). Divided into cases over and under 40 years old, the results were:

Over 40, males 9% of 139 cases: females 30% of 116 cases.
Under 40, males 12% of 72 cases; females 19% of 64 cases.

Antibody Titres in Thyroid and Non-thyroid Cases

One might reasonably expect to have found that the thyroid antibodies in non-thyroid cases were present in lower titre than in patients with thyroid disease. To some extent this was true (fig. 2). However, no sharp division could be made. A point about the 1/320 level would exclude three-quarters of the non-thyroid cases, but would also remove half of those patients with clinical thyroid disease.

TABLE II—NON-THYROID CASES TESTED BY THE TANNED-CELL HÆMAGGLUTINATION TECHNIQUE

Disease category	Male		Female	
	Total	Positive	Total	Positive
Syphilis	1	0	1	0
Tuberculosis, sarcoidosis	2	0	3	1
Bacterial infections	17	2	22	7*
Viral infections	21	2	14	4
Carcinoma, sarcoma	14	2*	17	7*
Reticuloses	1	0	4	0
Lymphatic leukæmia	1	0	1	0
Myelogenous leukæmia	1	0	1	0
Myelofibrosis	1	0	0	0
Para-, dys-proteinæmia	3	0	3	1*
Idiopathic acquired hæmolytic anæmia	1	0	2	1
Other anæmias	2	0	3	1
Disseminated lupus erythematosus	1	0	9	3**
Other "diffuse collagen" diseases	2	0	5	3
Rheumatoid arthritis	2	0	8	1
Asthma	6	0	2	0
Rheumatic fever	1	0	3	0
Glomerulonephritis	5	2	3	2
Nephrotic syndrome	2	0	3	0
Peptic ulcer, gastrointestinal hæmorrhage	13	0	6	1
Cirrhosis	18	3	6	2*
Acute hepatocellular disease	5	0	5	0
Diabetes	6	0	7	1
Addison's disease	0	0	1	1
Arteriosclerosis, atheroma, hypertension and sequelæ	32	6	18	5***
Miscellaneous and undiagnosed (see text)	50	5	32	5*
	208	22 (10·6%)	179	46 (25·7%)
Both sexes	Total 387			
	Positive 68 (17·6%)			

* See text.

All but 1 of the non-thyroid cases with titres of 1/5120 and above were women, and none was younger than 35 (average age 56). They are indicated by asterisks in table II. The conditions from which they were suffering are as follows: 1 male had carcinoma of the head of the pancreas; and the 10 females had severally shigella enteritis, carcinoma of the cervix, lymphoma with paraproteinæmia, disseminated lupus erythematosus (2 cases), active portal cirrhosis, hypertension in pregnancy, malignant hypertension, myocardial infarction, and senile osteoporosis. It may be that they had occult thyroid disease as well. On the other hand this incidence of high titres in women may mean only that they tend more than men to disease patterns involving serological disturbances, as in diffuse lupus erythematosus which is predominantly a disease of females and is associated with the appearance of irregular, exaggerated, or perhaps even irrelevant serum antibodies.

The blood donors comprised an equal number of males and females. The positive reactors (4 of whom were giving their first donation) were 2 males and 7 females aged (titres in brackets) 32 (40), 40 (40), (males); 26 (10), 33 (10), 34 (320), 37 (20), 43 (80), 44 (640), and 45 (20), (females).

Comment

The particular diseases from which our non-thyroid positive reactors were suffering (table II) are not predominantly diseases of women, and seem to bear no relation to what is known of thyroid function unless one considers that (as indeed is possible) this can be upset in any disease, past or present, with release of antigenic thyroglobulin. If this is the reason for the presence of the antibodies it carries the implication that 1 man in 10 or 1 woman in 4 in the medical beds of an Australian teaching hospital has or has had a disorder of the thyroid gland.

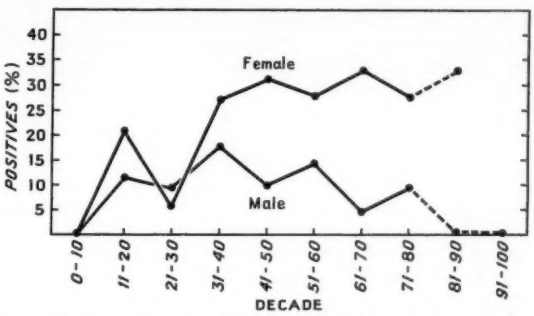

Fig. 1—Tanned-cell hæmagglutination (thyroglobulin). Non-thyroid cases. Relation to age.

The numbers of cases in each decade from which the percentages were calculated were:

	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100
Males	5	17	22	28	39	34	37	21	6	2
Females	3	19	16	26	29	29	30	22	6	0

As for their effects, one can only say from a clinical point of view that if thyroglobulin antibodies are found in the sera of as many as 18% of a large number of mixed medical patients who have not thyroid disease, then, whatever has provoked them, they are unlikely to be damaging the thyroid gland in any serious way, and it is quite possible that their role is physiological rather than pathological.

Goudie et al. (1959) tested the sera of 486 hospital patients without clinical thyroid disease. Using complement-fixation with thyrotoxic antigen, they found 6.8% positives, with some additional weak reactors. When analysed by sex and age most of those giving definite reactions were women over 50 years old. Necropsy studies showed a correlation between the presence of thyroid

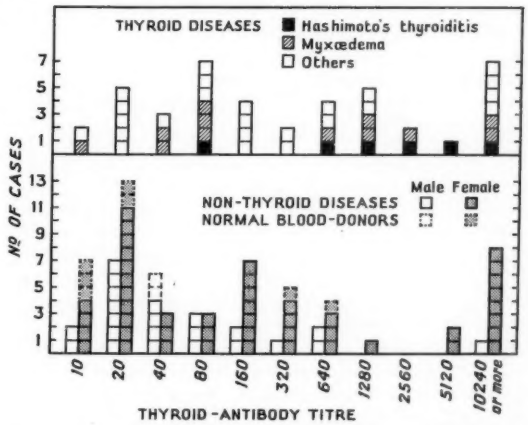

Fig. 2—Above: tanned-cell hæmagglutination (thyroglobulin) titres in 42 positives out of 69 thyroid cases tested. Below: the same in 68 positives out of 387 non-thyroid cases, and in 9 positives out of 102 healthy blood-donors.

antibody and the occurrence of mild Hashimoto-like histological changes in the gland, but this correlation was not absolute, a certain number of cases showing the changes in the gland without complement-fixing antibody in the serum. They report in the same paper that in 300 thyroid glands removed at necropsy from subjects over 40 years old the incidence of lymphocytic infiltration was 6% of 130 males and 30% of 148 females. The incidence of positives in persons over 40 in our series is similar to this (9% and 30% respectively). Possibly a finding of thyroglobulin antibodies indicates this histological condition in a person without clinical thyroid disease.

Summary

The sera of 69 cases of thyroid disease, and of 387 mixed cases without thyroid disease, were tested by the tanned-cell hæmagglutination technique for thyroglobulin antibody. Positive results were obtained in 59% of the thyroid cases and in 18% of the cases without thyroid disease.

We wish to thank Professor Robson and other consultants of the Royal Adelaide Hospital for allowing us access to their cases; Dr. Kathleen Maros for help with the sorting and recording of case-histories; Mrs. Stuart of the Walter and Eliza Hall Institute, Melbourne, for showing M. B. her tanned-cell hæmagglutination technique; and Miss N. Deering, and Miss B. Rainsford for valuable technical assistance.

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HYDROCORTISONE BY INHALATION
EFFECTS ON LUNG FUNCTION IN BRONCHIAL ASTHMA

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THE long-term use of systemic cortisone in the treatment of bronchial asthma may cause adrenal suppression and undesirable side-effects. It has been suggested that hydrocortisone by inhalation may act locally in smaller dosage, and favourable results have been reported in double-blind trials by Brockbank and Pengelly (1958) and Helm and Heyworth (1958). These workers, however, made no objective measurements of lung function, which are surely desirable in asthma, particularly when the therapeutic substance is known to have a tonic action.

In his trial of hydrocortisone hemisuccinate given by inhalation to asthmatic children Morrison Smith (1958) measured the forced expiratory volume, and did not find any significant improvement. But Brockbank and Pengelly (1958), also found hydrocortisone hemisuccinate ineffective. They attributed their success with the acetate to its being less soluble and therefore likely to be in contact with the bronchial mucosa for a longer period.

In our double-blind trial of hydrocortisone acetate given by inhalation to asthmatic adults, we have measured three aspects of lung function particularly affected by asthma: (1) the degree of hyperinflation of the lungs, (2) the ventilatory capacity of the lung, which varies with the resistance of the airways to air-flow and, (3) the evenness of distribution of inspired air, which is affected by unequal bronchial obstruction due to viscid sputum.

Methods

Ten patients with chronic asthma of moderate severity were studied. They did not have much seasonal variation, but five of them had histories of hay-fever, vasomotor rhinorrhœa, infantile eczema, or allergy to inhalants. Although some were thought to have underlying emphysema, all had definite evidence of reversible bronchospasm as judged by an increase of expiratory flow-rate after the inhalation of 1% isoprenaline. None had been on any steroid therapy for 1 month before the trial. During the trial they were allowed to continue with their usual remedies.

Hydrocortisone acetate was administered as a micronised powder of 3–5 μ particle size by the ' Medihaler ' apparatus of Riker Laboratories Ltd. The powder is suspended in an inert liquid under pressure. When the valve is depressed, a given volume containing 1·5 mg. of hydrocortisone acetate is released. The liquid vaporises at atmospheric pressure and leaves the finely suspended powder to be inhaled. The placebo consisted of the liquid without the powder. Each patient had 5 " puffs " night and morning, which is equivalent to 15 mg. of hydrocortisone per day. Initially the patients were given careful instruction and supervision in the method of administration.

The trial was controlled by the hospital pharmacist. Each patient inhaled the drug for a month, and the placebo for a month, six patients starting with the drug and four with the placebo.

Lung-function tests

Lung volumes.—The vital capacity (V.C.) was measured every week. The functional residual capacity (F.R.C.), which is the volume of the lungs at the end of a normal expiration, was measured every 2 weeks by the gas-dilution method of McMichael (1939). From these were obtained the residual volume (R.V.), which is the volume of the lungs at the end of maximal expiration, by subtracting the expiratory reserve volume from the F.R.C. (F.R.C. − E.R.V. = R.V.) and the total lung capacity (T.L.C.) which is the volume of the lungs at full inspiration (R.V. + V.C. = T.L.C.).

Ventilatory capacity.—The indirect maximum breathing capacity (Ind. M.B.C.) was calculated by measuring the volume of gas expelled in the first $^3/_4$ sec. of a forced expiration, and multiplying by a factor of 40.

The maximum expiratory and inspiratory flow-rates (M.E.F.R. and M.I.F.R.) were obtained spirometrically by measuring the time taken to deliver the litre of gas between the first 200 ml. and 1200 ml. of a forced expiration or inspiration respectively. This has the accuracy of an electrical pneumotachograph if a suitable spirometer and fast kymograph are used (Comroe et al. 1955) These measurements were made every week.

Evenness of distribution of inspired air.—This was measured every 2 weeks by the single-breath method of Comroe and Fowler (1951). If a single breath of oxygen is taken into the lungs of a normal subject, it is evenly diluted by the nitrogen already there. An instantaneous analysis of the concentration of nitrogen at the lips during expiration then provides a measure of the evenness of the dilution. Once the dead space is washed out, a plateau level of nitrogen is quickly reached. If more

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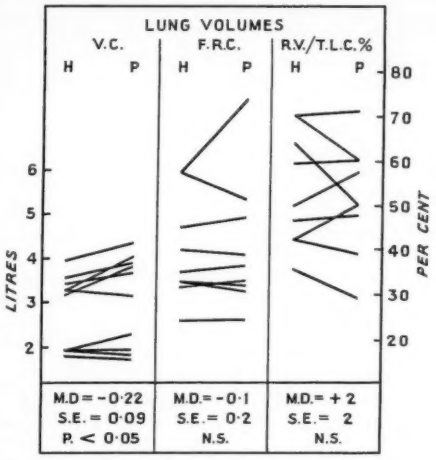

Fig. 1—M.D. = group mean difference between periods of hydrocortisone (H) and placebo (P). S.E. = standard error of difference.

inspired oxygen goes to some areas than others, the concentration of nitrogen rises throughout expiration as the areas which received little inspired oxygen contribute higher concentrations of nitrogen. The slope of the expired-nitrogen concentration is thus a measure of evenness of distribution of inspired oxygen. Normally the nitrogen concentration should not rise more than 2% between 750 and 1250 ml. of the expirate.

Expired nitrogen was measured instantaneously by a nitrogen meter sampling at the lips. This meter was designed

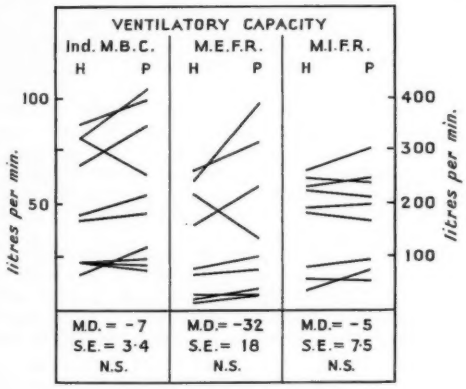

Fig. 2.

by Lilly (1950) and it depends on the activation of a photoelectric cell by the red glow of nitrogen in a vacuum tube.

Results

The clinical details of the patients and their own assessment of the treatment are shown in the table. Four thought they were better on hydrocortisone, one on the placebo, and five noticed no difference. There was no correlation between the subjective assessments and the objective tests.

Lung volumes.—The changes in the mean values of V.C., F.R.C. and R.V./T.L.V. % for the two periods are shown in fig. 1.—The V.C. shows a slight but statistically significant reduction in mean value during the hydrocortisone period ($P < 0.05$). The differences in mean values for F.R.C. and R.V./T.L.C. % are not significant.

Ventilatory capacity.—The changes in mean values of Ind. M.B.C., M.E.F.R. and M.I.F.R. shown in fig. 2 are not significant, although they are less during the hydrocortisone period.

Distribution of inspired gas.—The changes in mean values in the eight patients in whom this was measured are seen in fig. 3. There is no significant difference in the group mean for each period.

Discussion

The fact that there was no correlation between the subjective assessment of the patients and the objective tests of lung function confirm the necessity for the latter.

Thus there was no evidence that hyperinflation of the lungs was reduced, since neither the resting lung volume (F.R.C.) nor the ratio of residual volume to total lung capacity (R.V./T.L.C. %) was reduced. The vital capacity (V.C.) was actually less during the hydrocortisone period, suggesting that further areas of lung were obstructed during this period, and it is interesting that although changes in ventilatory capacity were not significant they were in the same direction.

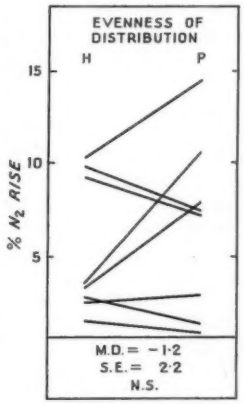

Fig. 3.

It is possible that particles of powdered hydrocortisone acetate actually caused an increase in airway resistance by irritation. Dubois and Dautreband (1958) have detected an immediate increase in airway resistance (using the body plethysmograph) after inhalation of inert carbon particles in small quantities similar to those used in the trial.

It seems likely, although it is not known, that smooth-muscle spasm is evenly distributed in asthma. Mucosal swelling and secretion are much more likely to be patchy in distribution, with emphasis in different areas; but on the evidence of the single-breath test for distribution, no improvement in this was achieved by hydrocortisone.

It may be argued that hydrocortisone was not reaching the affected area because of inefficient administration by the patient. This criticism holds whenever inhalation therapy is used, and in each of these patients a clear improvement was obtained after the use of 1% isoprenaline by inhalation.

Steroid therapy is undoubtedly of value in asthma, but from this study we conclude that the clinician cannot rely on inhalation therapy to reduce the total dose, and that there is apparently no additional advantage from the topical effect of the drug.

CLINICAL DETAILS OF PATIENTS

Age/Sex	Duration of asthma (years)	Allergy	Daily sputum	Subjective assessment
26 F	From infancy	Yes	None	Better on H
61 M	20	No	1/3 oz.	Better on H
44 F	16	Yes	1/2 oz.	No effect
34 M	14	Yes	1 oz.	Better on H
49 F	12	No	None	No effect
51 F	20	No	None	No effect
17 F	From infancy	Yes	None	Better on H
23 M	From infancy	Yes	None	No effect
53 F	26	Yes	None	Better on P
59 F	20	No	1/2 oz.	No effect

H = Hydrocortisone acetate. P = Placebo.

Summary

The effect of hydrocortisone acetate by inhalation on the subdivisions of lung volume, ventilatory capacity, and evenness of distribution of inspired gas has been studied in ten patients with chronic bronchial asthma.

There was no evidence that any of these parameters were improved.

We are grateful to Prof. I. G. W. Hill and Prof. R. B. Hunter for allowing us to study their patients. Riker Laboratories Ltd. provided 'Medihalers' with and without hydrocortisone and cooperated willingly in the study.

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ACTION OF INSULIN ON THE RESPIRATION OF RAT SCIATIC NERVE

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DURING previous experiments on substrate utilisation by peripheral nerves of rats we noted some effects of insulin on nerve respiration (Heller and Hesse 1958, 1959). These observations have since been extended.

Until recent years most investigators confined their interest to the action of insulin on brain tissue. Elliott and Libet (1942) and Elliott et al. (1942) concluded that "insulin added *in vitro*, or administered to the animal, does not obviously affect the respiration rate of brain suspensions". It was known that insulin added in vitro enhanced the oxygen uptake of minced pigeon muscle (Stadie et al. 1940) but the exact relation of this action to the carbohydrate metabolism of muscle was still obscure.

In 1958 Rafaelsen reported that insulin in the incubation medium increased the glucose uptake of isolated pieces of rat spinal cord by 50%. He also showed that in alloxan-diabetic rats the spinal-cord tissue had a 25% decreased glucose uptake and that this was increased by addition of insulin to the medium. He briefly mentioned "a clear-cut effect of insulin on glucose uptake in isolated rat sciatic nerve" but gave no details.

Our results indicate that insulin, when added in vitro, is capable of increasing the respiration-rate of rat sciatic nerve, provided suitable substrate is available.

Methods

Adult Wistar rats (weighing 225±20 g.) were used. Sciatic nerves were obtained as previously described (Heller and Hesse 1959) and their oxygen uptake was measured by the standard manometric procedure.

Each nerve was placed in a Warburg flask containing 2 ml. of a calcium-free phosphate-buffered medium containing (in millimols per litre) NaCl 122, KCl 3, $MgSO_4$ 1·2, and sodium phosphate buffer 17·5, and gassed with oxygen. The initial pH of the medium was 7·8–8·0 and the respiration was measured over 180 minutes. The temperature of the water-bath was 37°C.

In some experiments glucose was dissolved in a further 0·5 ml. of medium and added at the start of the experiment to give a final concentration of 0·01 *M*. Similarly, crystalline zinc insulin was dissolved in 0·5 ml. of medium and added to give a final concentration of 0·08 units.

Sciatic nerves were taken from the following groups of rats:

1. Normal rats.
2. Rats were fasted for 24 hours and then given 25 units of crystalline zinc insulin intraperitoneally. After about 3 hours the animals were comatose and they were then killed by a blow on the head. In all comatose animals blood-sugar levels were consistently below 40 mg. per 100 ml. (normal blood-sugar level is 120 mg. per 100 ml.).
3. Rats were fasted for 24 hours and then given a single injection of 1 ml. of 2 *M* glucose (360 mg.) intraperitoneally, with 50% glucose solution available for drinking. These animals were killed $3^1/_2$ hours after the glucose injection.
4. As in experiment 2, except that, at the same time as the insulin injection, 1 ml. of 2 *M* glucose was given intraperitoneally, with 50% glucose for drinking. These rats did not become comatose and they were killed $3^1/_2$ hours after the injections.
5. A final group of rats were used in whom the sciatic nerves had been previously sectioned high in the thigh. After 8 days the distal degenerated segments were excised and their respiratory activity measured.

Results

The accompanying table shows the oxygen consumption after 180 minutes by rat sciatic nerves in the absence of added substrate (autoxidation) and in the presence of glucose or insulin or both.

The respiratory rate of normal rat sciatic nerve is stimulated by the addition in vitro of glucose or insulin. The levels obtained with glucose are higher than with insulin. Insulin has little or no effect in the presence of glucose.

Nerves obtained from rats which have been rendered comatose by the injection of insulin show a depression of their autoxidation-rates to about two-thirds of the normal rate. The oxygen consumption of these nerves is increased by the presence in vitro of glucose but not by insulin alone; but again insulin has no effect in the presence of glucose. The values obtained by the addition of glucose, or glucose and insulin, are, like the autoxidation-rates, about two-thirds of the normal.

The injection of glucose intraperitoneally into a normal rat raises the autoxidation-rate of nerves from that animal. This rate is not appreciably increased by the further in-vitro addition of glucose or insulin—but is increased by the addition in vitro of glucose and insulin together.

Rats which have been given insulin intraperitoneally but (because of the simultaneous administration of glucose) are not comatose, show results like those in the normal animal. The absolute values obtained are, in general, lower than the normal, reflecting an overriding depressant effect of the insulin administered in vivo.

Using nerves which have undergone wallerian degeneration, the autoxidation-rates are depressed when compared to normal. The addition of glucose and/or insulin in vitro gives results similar to those obtained from normal animals. As was previously demonstrated with nerves from comatose animals, the absolute levels of respiratory activity of the cut nerves under

EFFECTS OF ADDED GLUCOSE AND INSULIN ON OXYGEN UPTAKE OF RAT SCIATIC NERVES

Preparation	Autoxidation	Glucose	Insulin	Glucose+insulin
Normal	95±7 (*90*)	157±5 (*21*)	136±7 (*12*)	165±6 (*11*)
Insulinised comatose	72±7 (*80*)	116±2 (*6*)	74±6 (*13*)	119±9 (*7*)
Glucose (intraperitoneal)	132±3 (*6*)	135±6 (*6*)	130±3 (*6*)	155±5 (*6*)
Insulinised+glucose non-comatose ..	111±6 (*8*)	134±5 (*12*)	125±5 (*12*)	144±5 (*11*)
Neurotmesis* ..	68±8 (*80*)	116±16 (*8*)	93±6 (*6*)	135±5 (*8*)

* Eight days after nerve section.
Figures indicate the total oxygen uptake, ±standard deviation, in microlitres per 100 mg. wet weight after 180 minutes.
Figures in parentheses indicate the number of experiments.

each condition are only about two-thirds of the normal values, apparently because of the dropout of the contribution of the axis cylinder (Heller and Hesse 1959).

Conclusions

These results indicate that insulin, when added in vitro, is capable of stimulating respiration in the resting nerve, probably by enhancing the utilisation of glucose, endogenous or exogenous.

Insulin added in vitro cannot stimulate the respiratory rate of nerves obtained from rats in hypoglycæmic coma, probably because the endogenous glucose supply is depleted in these nerves.

Glucose given intraperitoneally stimulates respiration in the resting nerve, presumably by increasing the amount of endogenous glucose in the nerve. No further effect is seen with glucose or insulin added to the medium but some increase in the oxygen uptake is observed when glucose and insulin are added together.

In rats given insulin and protected by intraperitoneal glucose, the values obtained seem to reflect a balance between the depressing effect of insulin in vivo and the stimulatory effect of the intraperitoneal glucose: the autoxidation-rate is slightly increased, and further addition of glucose and/or insulin can stimulate the respiratory rate, but not to as high levels as is found in nerve from the normal animal.

We have no direct evidence that insulin, added in vivo or in vitro, can stimulate nerve respiration in the absence of endogenous or added substrate. Its failure to stimulate respiration when added alone to nerves derived from comatose rats suggests that its effect is exerted only on the metabolism of glucose.

Where glucose was given intraperitoneally, the autoxidation-rate was stimulated considerably and further addition of glucose to the medium was without effect. This suggests that the endogenous glucose level in the nerve had reached a high level, preventing further influx of glucose into the nerve. Similarly, the addition of insulin alone to the medium had no significant effect. However, when both glucose and insulin were added, there was a further increase in the respiratory rate, with values approaching those of nerves from the normal animal. It appears likely that the effect of insulin is due to some action on surface membranes of the nerve, permitting further entry of glucose.

Rafaelsen (1958) was also impressed by the necessity of having intact cell membranes in order to demonstrate an effect of added insulin. He was able to show that " insulin increases the glucose uptake of brain-cortex slices (having one intact pia-covered surface), whereas following slices (having two artificial surfaces) are uninfluenced by insulin ". He also emphasised that, in his experiments with rat spinal cord and sciatic nerve, the cell membranes were preserved. Candela and Martin-Hernandez (1959) have been unable to confirm the results of Rafaelsen with spinal cord except with tissue from animals anæsthetised with carbon dioxide. Our results with nerve are compatible with those of Rafaelsen but provide no evidence in confirmation of them.

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IMPROVED MATERIAL FOR RADCLIFFE TRACHEOSTOMY TUBE

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THE problem of tissue irritation is common to all tracheostomy tubes (Jacobs and Affeldt 1956). This irritation has been described with tubes made from polymers of high molecular weight—e.g., rubbers, polyethylenes, and nylons—and also with silver tubes. The latter have the additional disadvantage of rigidity, which leads to discomfort during movement of the head and neck. Here we discuss the possible nature of tissue irritation, describe a tube used to overcome it, and report an illustrative case.

Nature of Tissue Irritation

High polymers vary greatly in composition, and their properties are also modified by the addition of filler substances. These fillers, which are usually mineral, have three main functions: they facilitate extrusion, modify elasticity, and provide colour and reduce translucency.

Fillers are as likely to produce tissue irritation as the parent substances (Ellis and Siegel 1948, Mallette and von Haam 1952). The causes of tissue irritation may be broadly divided into physical and chemical:

Physical.—Some friction between a tracheostomy tube and the tissues of the neck is inevitable. The amount of irritation caused may well depend on the abrasive powers of the tube material. Certain fillers, especially those used in rubbers, are known to be abrasive outside the body. A study of the relation between the physical structure of various materials and tissue irritation is in progress (Little 1959). Rigid tubes, besides causing discomfort during movement of the head and neck, may cause areas of pressure necrosis at points of contact with the tracheal mucosa (Robin 1955, Jacobs and Affeldt 1956).

Chemical.—Some filler substances have bacteriostatic properties (Handfield Jones and Lewis 1955). The presence of such activity in the material of a tracheostomy tube is a possible cause of inflammatory reaction. Chemical irritation of the tissues may also occur independently of bacteriostatic activity. Dimant (1955), for example, believed that a constituent of silicone rubber had caused meningitis when tubing of this material was used to short-circuit an obstructive hydrocephalus. Ageing and degeneration of tubes may also occur within the body (Weizenblatt 1957).

Development and Description of Modified Tube

The design of the original right-angled Radcliffe tracheostomy tube described by Spalding and Crampton Smith (1956) has proved satisfactory. An increase of tracheal secretion, however, is often noted after its insertion, and, as with other types of tube, a variable degree of inflammatory reaction is seen in the skin adjacent to the stoma. In an attempt to overcome these disadvantages the composition of the tube was successively modified as follows:

Prototype A.—A standard Radcliffe tracheostomy tube was made of rubber which did not contain a bacteriostatic agent. Bacteriological examination showed, however, that the growth

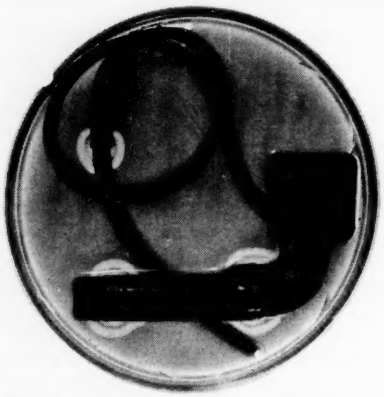

Fig. 1—Bacteriostatic action of parts of the tube.

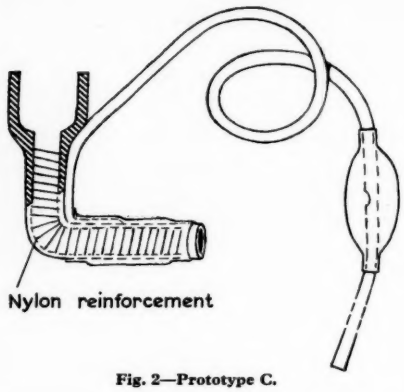

Fig. 2—Prototype C.

of bacteria was inhibited where the cuff and pilot balloon were sealed to the tracheostomy tube; this was due to bacteriostatic activity in the cement (fig. 1). The suppliers of the tube were unable to provide a cement with lower bacteriostatic activity.

Prototype B.—A prototype-A rubber tube was dipped with latex. Great care is necessary in this dipping process because the latex may peel off, and the method is not advised for commercial production. Furthermore, bacteriological examination showed that bacteriostatic activity was transmitted through the latex material from the underlying tube. Since whatever bacteriostatic activity was present in the prototype-A tube also infiltrated through the latex cover of the prototype-B tube, it seems reasonable to assume that any difference in tissue reaction produced by the two tubes would be due to differences between rubber and latex.

Our experience with the above tubes (see case-report), led to the production of *prototype C*. This is a latex tube with a spiral nylon reinforcement (fig. 2). Sanders (1947) produced an endotracheal tube from this type of material. Further work in the Nuffield Department of Anæsthetics over the last four years using wire, cotton-thread, or nylon reinforcement has resulted in the adoption of a modified nylon-reinforced latex tracheostomy tube. It is virtually "unkinkable" when in position and sufficiently elastic to avoid discomfort to the patient during movement. We have also found it to be non-irritant.

It should be mentioned, however, that the composition of latex is not constant. The antoxidants added by the grower before shipping may vary, as also may the chemicals used by different manufacturers in production. These are usually removed by the process of "leaching", but it is possible that batches of latex may differ in respect of their irritative properties.

Case-report

In July, 1958, a man aged 32 was admitted to the respiratory unit of the Churchill Hospital with acute bulbar and respiratory poliomyelitis. Tracheostomy was performed and one of the original Radcliffe rubber tracheostomy tubes was inserted.

After three weeks, swallowing was normal, and the patient no longer forced saliva and pharyngeal contents into his trachea to leak out through his tracheostome. The moist and infected area which had developed around the mucocutaneous junction of the stoma did not clear up with the return of swallowing and at its worst extended to the anterior chest wall, and was persistent.

In December, 1958, the Radcliffe rubber tracheostomy tube was replaced by a prototype-A tube. No improvement in the inflammatory reaction occurred in the succeeding four weeks.

In January, 1959, a prototype-B (latex-dipped) tube was inserted. Seven days later the patient's skin had completely healed. This tube remained in place for eleven weeks without any recurrence of tissue irritation. It was then removed because the pilot balloon of the cuff had deteriorated.

It was replaced by a prototype C (nylon-thread reinforced latex tube). The patient found this more comfortable than any previous tube because of the absence of discomfort during head movement. This tube was unfortunately too long, and after three weeks it was removed. It was replaced by a prototype-A tube, no more nylon-reinforced latex tubes being available at that time. During the following week the skin remained intact and there was no increase in tracheal secretions. After ten days, however, the skin broke down again, though the tracheal secretions did not increase. Another prototype-B (latex-dipped) tube was substituted and the skin healed within a week. Some three weeks later nylon-reinforced latex tubes became available and the patient's skin remained healed.

Discussion

The amount of bacteriostatic activity present in the cement used to seal the cuff and pilot balloon to the A and B tubes was common to both. The tissues broke down with tube A and healed with tube B. Hence, bacteriostatic activity was probably not the cause of breakdown in this patient. Similarly, absence of tissue irritation with the modified nylon-thread reinforced latex tube was not due entirely to reduced rigidity, since a standard rubber tube overdipped with latex was also non-irritant.

There remain two possible explanations for the tissue irritation in this case:

(a) *Chemical irritation other than that due to bacterial inhibitors.*—This seems unlikely since the tube made from rubber without bacteriostatic activity (prototype A) did not provoke any increase in tracheal secretions.

(b) *Irritation due to the physical characteristics* (e.g., abrasive qualities of the tube).—This seems at the moment to be the most probable explanation.

The problem of tissue reaction to foreign materials is not confined to tracheostomy. Complications have occurred with Mousseau-Barbin œsophageal tubes and with silicone rubber tubes (Dimant 1955). Rubber Hodge and ring pessaries may cause vaginitis and ulceration of the mucous membrane (Jeffcoate 1957). These reactions may be related to the use of unsuitable materials.

Many high polymers in present-day use are not made specifically for medical purposes, and they may be unsuitable for clinical use. Further work on this problem will be forthcoming.

Summary

Tracheostomy tubes irritate the tracheostome and the mucous membrane of the trachea. The mechanism of this is discussed.

An improved material, latex rubber reinforced with nylon thread, is described for use in making tracheostomy tubes. A Radcliffe tracheostomy tube of this material has been used with encouraging results.

Our thanks are due to Sir Robert Macintosh for his encouragement, and to Dr. W. Ritchie Russell for permission to publish his

case; to Dr. A. Crampton Smith and Dr. J. M. K. Spalding for helpful advice on the design of the tracheostomy tube; to Dr. Crampton Smith and Dr. H. G. Epstein for constructive criticism of this paper; to Dr. R. L. Vollum for the bacteriological studies; to Dr. K. Little for help and advice on the structural composition of polymers; and to the Leyland and Birmingham Rubber Company for manufacturing the tubes, which are available from the Mitcham Rubber Company Ltd.

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Preliminary Communications

CHROMOSOMAL TRANSLOCATIONS IN MONGOLISM AND IN NORMAL RELATIVES

THE suggestion that mongolism is associated with a chromosomal aberration was made by Waardenburg in 1932 [1] and non-disjunction was specifically mentioned. Last year, in reporting their finding of trisomy, Lejeune et al.[2] said that this could be caused by non-disjunction facilitated by advancing maternal age. Investigation of familial examples, however, shows the presence of a group in which maternal age is not an appreciable ætiological factor and in which transmission is usually through the mother (Penrose [3]). In view of the work of Snell, Bodemann, and Hollander [4] on hereditary malformations in mice, it seemed likely that translocation of chromosomes would best explain this familial pattern (Penrose [5]). A translocation in mongolism was recently reported by Polani et al.[6]; cells from bone-marrow of a female aged 10 showed fusion of two chromosomes—nos. 14 and 21 in the Denver nomenclature. Fraccaro et al.[7] found unusual chromosomes in bone-marrow and skin cultures from a male mongol aged 5 months; an extra chromosome was seen in most cells of a skin culture from the father. The present communication describes translocations occurring in three patients, two of whom are sibs.

PATIENT A is a male, aged 48, who is a healthy, characteristic mongol imbecile. The father, now dead, was 41 at the patient's birth and the mother was 33. There is one healthy female sib aged 50; her karyotype was examined but no abnormality was detected.

A culture from a skin biopsy, taken from the patient in 1959, revealed that only 46 chromosomes were present. The karyotype appeared similar to that reported by Fraccaro et al.[7]: it was deficient in two small acrocentric chromosomes and had an extra small metacentric chromosome. Biopsy from the right

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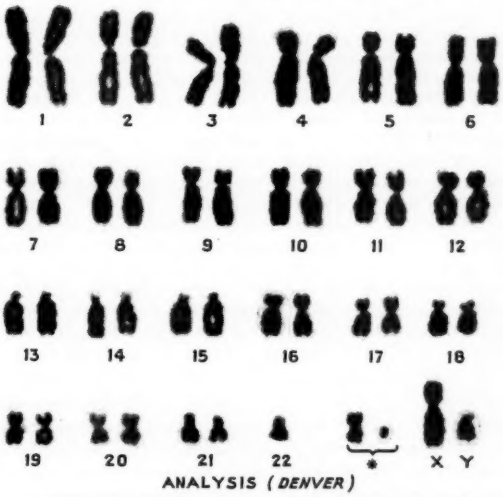
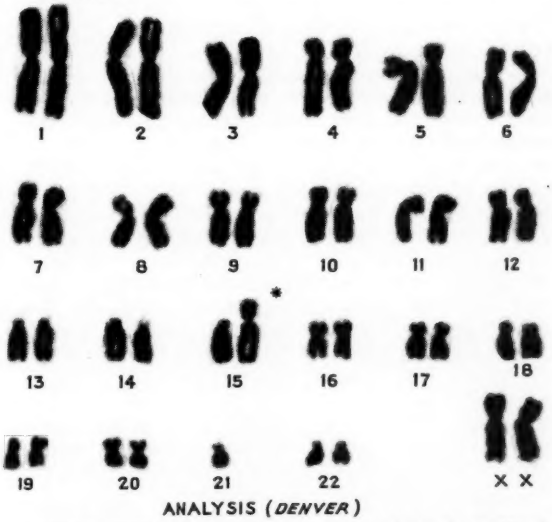


* Assumed to be reciprocal translocation of a no. 21 and a no. 22.

Fig. 1—Somatic chromosomes in a dermal-cell culture from patient A.

CELL



* This chromosome is assumed to have been formed by fusion of a no. 15 and a no. 21.

Fig. 2—Somatic chromosomes in a dermal-cell culture from the mother of patients B and C.

testis indicated that spermatogenesis was fairly active in the early stages; at diakinesis fewer than the normal number of 23 masses were identified and it was thought that a quadrivalent could be seen in some cells.[8] In the culture from a second skin biopsy, taken in 1960, the cytological peculiarity previously found was again present, but this time it was noticed that some cells contained an additional minute, Feulgen-positive, centric particle (see fig. 1). In some cells three small acrocentric chromosomes were clearly satellited. Although this suggests that the extra metacentric had arisen through union between two no. 22 chromosomes, this was not regarded as conclusive since recent findings of many workers suggest that both chromosomes 21 and 22 may be satellited. Moreover, the report of a quadrivalent during meiosis suggests that the extra metacentric had arisen by a reciprocal translocation between chromosomes 21 and 22, the other product being an unstable minute centric fragment. Since this had not been eliminated from all cells, the translocation is thought to have been of relatively recent origin.

PATIENT B, a female aged 8, is a healthy, typical mongol with intelligence above the average level for such children. At the time of her birth the father was 21 and the mother 23 years old.

There are two surviving sibs, a normal girl aged 6 and patient C; also there were two miscarriages.

Cells cultured from a skin biopsy showed a complement of 46 chromosomes. Among these were only five large acrocentrics (group 13–15), four small acrocentrics (group 21–22), and an extra chromosome in the group 7–12. The extra chromosome was thought to have arisen by fusion of major portions of a no. 15 and a no. 21.

PATIENT C, a male aged 2 years and 8 months, is affected typically with mongolism; though much retarded, he is healthy and alert. Cells in culture, derived from skin biopsy, show a complement of 46 chromosomes. As in cells from patient B, there were only five large acrocentrics and one extra chromosome in the group 7–12. There were five small acrocentrics present, one of which was assumed to be the Y-chromosome.

Five normal and healthy members of the family of patients B and C have been tested by culture from skin biopsy. The cells from the father showed no abnormality of karyotype, nor did those derived from the patients' mother's father. However, skin-biopsy cultures from the mother herself, her own mother, and her own normal daughter all showed the same peculiarity. In every cell studied the number of chromosomes was 45. There were only five large acrocentrics in group 13–15, three small acrocentrics in group 21–22, and one extra chromosome in group 7–12 (see fig. 2).

The simplest interpretation of the cytology in this pedigree is that a reciprocal translocation, involving a no. 15 and a no. 21 chromosome, occurred in an ancestor on the female side. A centric fragment has since been lost and the large fused chromosome has been transmitted through several generations of normal individuals. These normals with the translocation can produce unbalanced gametes which contain excess or deficit of chromatin belonging to the pair of chromosomes concerned. Mongolism in these patients B and C has thus been caused by fertilisation by normal sperm of unbalanced ova containing nearly double quantities of chromosome no. 21. The result is a condition in the zygote which is almost equivalent to the trisomy of no. 21 found in most cases of mongolism.

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PITUITARY RESPONSIVENESS TO STRESS AFTER CORTICOID THERAPY

THE impairment of corticoid response to stress after corticoid therapy and the adrenal component in this have been well established.[1] It is proposed to show the importance of a pituitary factor; and a new method of testing pituitary function will be described.

Hyalinisation of pituitary basophil cells following the use of corticoids has been described, first in animals by Laqueur [2] and later in man.[3–5] Such hyalinisation has also been reported after corticotrophin [3 5 6]—a month later in one patient,[5] and as long as fifteen months in another.[3] Collapse following stress has been reported after corticotrophin in animals [7] and in man [8–12]; if anything the adrenal cortex will be hyperplastic in these subjects.

The adrenocorticotrophic centre in the hypothalamus [13] may be concerned in "pituitary" response. Damage to cells of the paraventricular nucleus in rats after corticotrophin has been reported.[14]

It seemed worth while developing a test for pituitary responsiveness to stress, and applying it to series of patients on corticoid and corticotrophin therapy, and of controls.

METHODS AND MATERIAL

The stressing agent employed was a pure crystalline protein-free pyrogen prepared from a strain of *Proteus vulgaris* by Prof. J. R. Todd. This is active in minute quantities (0·005 μg. per kg.) and has an M.L.D.$_{50}$ dose some 1000 times the pyrogenic dose. "Pituitary" response was assessed by comparison of twenty-four-hour excretion of 17-ketogenic steroids before and after injections of pyrogen. Neutral-17-ketosteroid responses were also studied but proved unhelpful. Various dosages, intravenous and intramuscular routes, and various urinary collection schedules were tried. Eventually the test was standardised at intravenous injections of 0·005 μg. per kg. with urinary collections one day before and two days after the injections. Oral temperatures were recorded half-hourly for the first four hours, and hourly for a further six hours. Urinary 17-ketogenic steroids were determined by the method of Norymberski et al.[15]

Tests were carried out on two groups of patients. The first consisted of 10 patients on corticoid therapy and 6 on corticotrophin. In these patients treatment was stopped and tests were carried out one week later. The second group consisted of 17 patients who, as far as was known, had never been given corticoids nor corticotrophin. Two-thirds of the patients in both series had rheumatoid arthritis.

RESULTS

The 17-ketogenic-steroid responses for the two series are contrasted in the accompanying table and figure. In the figure the response is expressed as a percentage rise above the resting level in the first twenty-four hours after injection. The figure suggests an impairment of response in the post-corticoid series; the difference between the means of the two series is statistically significant at the 5% level.

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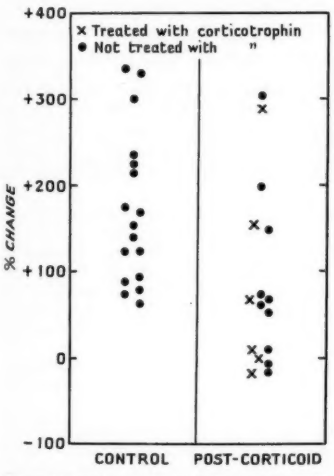
URINARY 17-KETOGENIC EXCRETION (MG. PER 24 HOURS) BEFORE AND AFTER ADMINISTRATION OF PYROGEN

Controls			Post-corticoid		
Case no.	Before	After	Case no.	Before	After
A	19·2	31·4	1	13·3	11·1
B	19·8	35.0	2*	29·6	26·4
C	17·0	30·6	3	5·7	5·5
D	27·7	34·2	4*	18·9	19·6
E	18·8	36·8	5*	9·8	11·0
F	5·4	12·2	6	10·2	11·0
G	17·0	38·6	7	12·9	20·0
H	17·2	41·1	8	17·0	27·9
I	8·8	22·6	9	19·6	32·6
J	10·1	27·1	10*	9·6	16·3
K	13·2	36·4	11	13·1	23·2
L	12·3	38·8	12	16·2	40·1
M	10·2	33·0	13*	11·5	40·7
N	11·8	39·8	14	15·7	47·0
O	3·2	12·8	15*	16·8	65·4
P	10·8	46·8	16	17·7	72·0
Q	11·0	48·1			

* Treated with corticotrophin.

Response in 6 of the post-corticoid subjects was negligible, lying between +15% and −15%, the lowest control response being +65%. It is particularly important that 3 of these subjects had been receiving corticotrophin. 2 of the 6 showed a response in the second twenty-four hours after injection. A similar lack of responsiveness, and delayed responses, have been observed by Engel et al.[16] and Melby [17] respectively.

A good deal of individual variation in febrile response between patients was observed. Maximum temperatures ranged between 99·4° and 104°F. The duration of response also varied, but the maximum temperature was commonly reached in three to four hours, and the response usually lasted for from six to eight hours. There was a tendency for 17-ketogenic - steroid excretion response to correlate with the height of fever, but again there were considerable individual variations.



Percentage change in 17-ketogenic steroid excretion after administration of pyrogen.

Observations on return of pituitary responsiveness were made on 5 out of 6 post-corticoid patients showing negligible responses. Patients were first tested at weekly intervals. Responsiveness had returned in 2 on second testing. It was still absent in a 3rd at the end of one month; this patient was retested one month later when some responsiveness had returned. The other 2 were retested only once, response still being impaired.

COMMENT

The negligible responsiveness in the 3 patients treated with corticotrophin supports the published evidence that there is a " pituitary " factor in the lack of responsiveness to stress in corticoid-treated patients. This may account for the experiences of Hayes [9] and Hayes and Kushlan.[10] These workers tested responsiveness to corticotrophin before operation in patients who had previously received corticoid therapy. Those with poor reactivity were treated with daily injections of corticotrophin until the response was within normal limits. Collapse followed surgery in some patients. It is probably unwise to use corticotrophin in an attempt to restore responsiveness after corticoid therapy.

Pyrogen injections may prove of practical value in restoring responsiveness.

The test for pituitary responsiveness to stress described here may be useful in other conditions where the pituitary is thought to be involved. We found this test helpful in 2 cases of suspected panhypopituitarism. Melby [17] also reports favourably on its use in panhypopituitarism.

16. Engel, E., Loizeau, E., Riondel, A. M. *Rev. franç. Etud. clin. biol.* 1959, **4**, 498.
17. Melby, J. C. *J. clin. Invest.* 1959, **38**, 1025.

We wish to thank all those who have helped us in this investigation, and in particular Dr. W. J. Tindall of Organon Laboratories for a supply of the pyrogen, Mr. M. P. Curwen for advice on statistical aspects, and Dr. E. F. Scowen for guidance. One of us (B. P.) was in receipt of a grant from the North East Regional Hospital Board, which is gratefully acknowledged.

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New Inventions

A NEW METHOD OF OXYGEN DETERMINATION

THIS method of oxygen determination is based on a newly discovered principle of " potential interruption ", using a platinum microelectrode as a capacitor.[1] The method may have wide medical applications. The apparatus (fig. 1) can be used for oxygen determinations in both gas and liquid systems, and in particular for measuring oxygen in biological fluids, such as saliva and blood.

The basic principle on which the instrument works is the measurement of the amount of charge lost by a solid microelectrode through electrochemical reduction of oxygen at the electrode surface. This loss of charge is related to the oxygen tension of the fluid in which it is immersed.

As shown in fig. 2 the electrode is permanently immersed in a small quantity of saline enclosed by a ' Teflon ' sheet across which oxygen diffuses into the saline. The membrane can be brought into contact with either a gas or a liquid; and, since the dimensions are small, and teflon is permeable to oxygen only, the tensions of this gas will rapidly reach the same

1. Glover, J. H. Proceedings of 2nd International Congress of Polarography, 1959 (in the press).

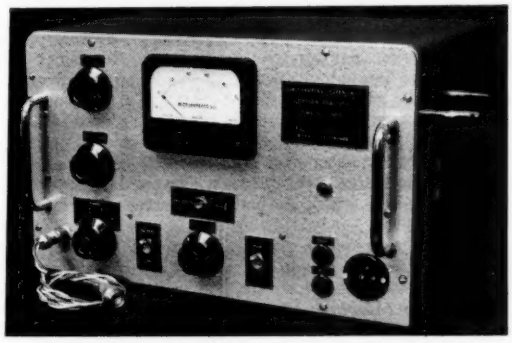

Fig. 1—The potential-interruption oxygen analyser.

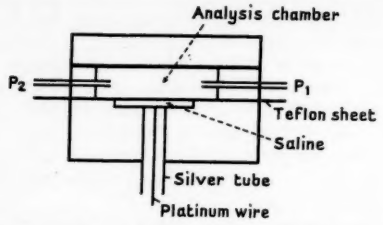

Fig. 2—Schematic diagram of the electrode and analysis cell.

value on either side of the membrane. It is the oxygen concentration in the saline which is measured.

Because the signal from the electrode is virtually independent of size the apparatus can be very small; at the same time the signal can be measured on a simple and robust device.

PRELIMINARY EXPERIMENTS

Determination of Oxygen in Gases

Gases of various known oxygen content were introduced into the analysis chamber of the electrode, or alternatively the top of the chamber was removed and the system introduced directly into a gas line. The readings given on the meter of the analyser were noted and plotted against the oxygen concentration, giving a calibration curve. Three observations were made: (1) in the absence of oxygen a small reading was obtained; (2) the calibration curve was not quite linear; and (3) the temperature coefficient was about 1·5% per °C. This last observation means that for accurate work the electrode must be held at constant temperature or a compensating system must be introduced.

Having been calibrated, the apparatus was used to measure the oxygen concentration in a number of gas mixtures whose oxygen content was independently measured by a mass spectrometer. The results are shown in the table.

COMPARISON OF RESULTS OF OXYGEN ANALYSIS BY POTENTIAL INTERRUPTER AND BY MASS SPECTROMETER

Sample	Oxygen (% v/v)		
	By mass spectrometer	By potential-interruption oxygen analyser	Error
3/1	28·5	27·0	1·5
3/3	23·4	23·8	0·4
3/4	20·9	20·5	0·4
4/1	28·0	27·3	0·7
4/2	27·0	26·5	0·5
4/3	26·8	26·0	0·8
4/4	21·3	20·9	0·4
5/1	26·1	26·4	0·3
5/2	25·4	25·0	0·4
5/3	25·1	25·0	0·1
5/4	21·0	20·5	0·5

Since the apparatus might be of value in anæsthesia the possibility of interference by anæsthetic gases was investigated. The oxygen measurements were not affected by ether, cyclopropane, trichlorethylene, or nitrous oxide.

Determination of Oxygen in Liquids

With saline containing a known partial pressure of oxygen in the analysis chamber, the readings on the meter were within 2% of those obtained with the same partial pressure of oxygen in the gaseous phase.

The measurement of oxygen in blood is theoretically more difficult, and three sources of error are possible: (1) electrode poisoning due to substances in the blood; (2) errors due to inadequate definition of the diffusion layer; and (3) the presence of red blood-cells which are potential sources of, or absorbents for, oxygen.

Since the electrode is protected from the blood by teflon, as in the Clark electrode,[2] it seemed probable that blood would not poison the electrode, and in practice it was found not to do so. Moreover, since oxygen is measured in the saline around the electrode the other difficulties might not arise.

2. Clark, L. C. *Trans. Amer. Soc. Anat. intern. Org.* 1956, 2, 41.

Experimentally it was found that if the layer of saline was too thin, the results with blood were erratic and variable. If red cells were allowed to fall slowly on to the membrane the readings fell progressively. If the saline layer was at least 0·05 mm. thick, however, the readings were constant, being within 5% of those obtained with saline or air which had the same partial pressure of oxygen. This discrepancy is greater than that between air and saline, and we think it is due to inadequate mixing of the blood samples in the chamber. A new chamber is being constructed for blood.

Characteristics of the Apparatus

The potential interrupter is (1) sensitive to 0·02% oxygen, (2) accurate in the range 0–40±2% (except for blood), and (3) capable of responding within 14 seconds.

CONCLUSIONS

This electrode system is simple and robust, and it gives moderately accurate results. Since it can be made very small it might be used on a cardiac catheter, and possibly in tissues. Its rather long response-time may preclude some applications; but this is due to the time-cycle of interrupted application of potential, and could be substantially reduced.

The instrument has been developed in the laboratories of British Oxygen Research & Development Ltd.

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APPLICATION OF ENDORADIOSONDE OR "WIRELESS PILL" TO RECORDING OF UTERINE CONTRACTIONS AND FŒTAL HEART-SOUNDS

"WIRELESS pills" (Medical Research Council design *)[1] were introduced into the uterine cavity, external to the membranes, of three patients at surgical induction of labour. They were introduced held in a minute cylindrical cup screwed to the end of a Drew-Smyth catheter, and ejected from the cup with the stilette.

The wireless pill is a small radio-frequency (0·4 Mc/s) transistorised transmitter with self-contained battery and switch. It is hermetically sealed in 'Perspex'. It is cylindrical, 0·35 in. (9·0 mm.) in diameter, and 0·76 in. (19·3 mm.) long. It can be sterilised chemically. The frequency of the device is varied by the external hydrostatic pressure and it will transmit continuously for 24 hours. The pills are switched on by shaking prior to insertion, and after recovery can be switched off and reclaimed for further use.

A thread was attached to the pills to ease removal. After parturition one was expelled spontaneously. The other two were removed before the second stage of labour by gentle traction on the thread.

* Manufactured by The Solarton Electronic Group Ltd.

1. Rowlands, E. N., Wolff, H. S. *Brit. Commun. Electron.* 1960, 7, 598.

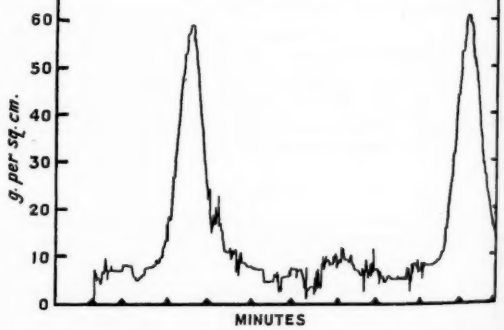

Fig. 1—Recording of amniotic-fluid pressure during labour.

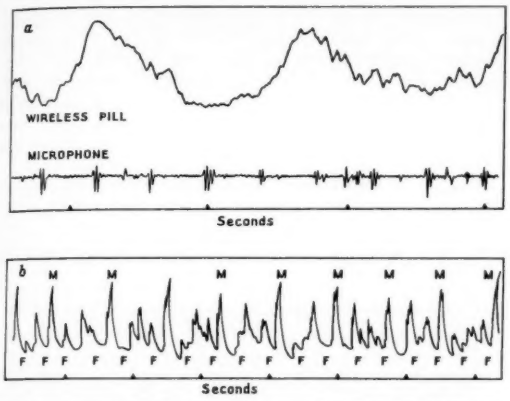

Fig. 2 (*a*)—Upper trace: Composite record of low-frequency pressure fluctuations, maternal respiration, and maternal and fœtal heart-sounds. Lower trace: Recording obtained by means of a microphone.

(*b*)—Maternal and fœtal heart components derived from fig. 2*a* by means of frequency discrimination. F=fœtal heart-beat; M=maternal heart-beat.

The pressure range of the pill is 0–100 g. per sq. cm. and uterine contractions change the frequency by as much as 30 Kc/s. The radiowaves transmitted are detected by a nearby aerial and wireless receiver and passed to a chart recorder.

Fœtal heart-beats cause a frequency change of only a few cycles per second, but such variations are readily detected by the heterodyne method and a sensitive frequency meter.

A section of the recording of the amniotic-fluid pressure is reproduced in fig. 1. Incremental frequency changes are shown in fig. 2a where waves representative of maternal respiration, maternal heart-sounds, and fœtal heart-sounds are superimposed on larger and much lower frequency pressure changes. Fig. 2b shows these same wave forms after frequency discrimination; the maternal heart-sounds are obscuring easy interpretation of fœtal heart-rate. It is hoped that further improvements to the endoradiosonde and frequency analyser will result in more complete separation of the fœtal heart components.

The wireless pill offers possibilities for extending obstetric research and treatment control. The patient is free to move about or even to walk around, and observations can continue without disturbing her if she sleeps in her most comfortable position. Further, it dispenses with the abdominal belts which hold tocographs and microphones in position and interfere with the free movement of the uterus. Recordings can also be made from a patient while being treated in the Heyns decompression suit in which the abdominal wall is drawn away from the uterus, precluding conventional auscultation and tocography during contractions.

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Reviews of Books

The Sturge-Weber Syndrome

G. L. ALEXANDER, M.D., F.R.C.S., surgeon-in-charge, department of neurological surgery, Frenchay Hospital, Bristol; R. M. NORMAN, M.D., M.R.C.P., research consultant in neuropathology, South-Western Regional Hospital Board, Burden neuropathological laboratory, Frenchay Hospital, Bristol. Bristol: John Wright. 1960. Pp. 104. 32*s*. 6*d*.

THIS monograph, by a neurosurgeon and a neuropathologist, is dedicated to Dr. Parkes Weber " in his ninety seventh year ". The authors, themselves working in Bristol, recall that W. A. Sturge was born in Bristol in 1850, and he described the syndrome in 1879 before the Clinical Society of London. His patient, who showed the characteristic facial nævus and buphthalmos, also suffered from epilepsy and hemiparesis.

The authors record seven case-histories of the Sturge-Weber syndrome. The essential features are cutaneous facial angiomatosis (always extending above the palpebral fissure) and gyriform calcification (radiographically apparent after the age of two years) underlying an area of leptomeningeal angiomatosis which is unilateral and usually confined to the posterior half of the brain. Mental retardation and epilepsy are common together with buphthalmos and hemiparesis. The authors deny that there is any association between the site of the facial lesion and the distribution of the trigeminal nerve. They agree with Rønne (1937) that the disease has its origin at a time in the early development of the embryo when the ectoderm which later forms the skin of the upper part of the face overlies the area of the neural tube which is to form the occipital and adjacent parts of the cerebrum. They regard the calcification as the result of a local change in tissue metabolism, possibly secondary to hypoxia caused by the angiomatosis. The neuronal destruction is caused by the calcification, but epilepsy may also be a contributory factor. Since the epilepsy seems to result in mental deterioration and paralysis, the authors recommend lobectomy (or the removal of the area affected) at the age of two months.

This is an admirable monograph, in which the clinical studies are well supported by psychiatric, electroencephalographic, and pathological investigations. It is beautifully produced and the photographs are excellent.

Handbook of Hæmatological and Blood Transfusion Technique

J. W. DELANEY, F.I.M.L.T., chief technician, Laboratories of the Westminster Hospital, London. London: Butterworth. 1960. Pp. 311. 45*s*.

THIS book is designed to cover the syllabus of the Institute of Medical Laboratory Technicians examination, and it does so very effectively. The many procedures are clearly described in proper detail and step by step. The list of tests is notably complete, including tests used in the investigation of rheumatic and allied diseases such as the Rose-Waaler test. As well as the sections on technique there are chapters containing brief accounts of such basic matters as " the origin, life and death of the blood cells ", " the cell and inheritance ", and some chapters begin with accounts of pathological states in hæmatology and the background to the tests used. These accounts are necessarily very compressed and contain some doubtful statements presented as established facts. But the section on hæmorrhagic and purpuric disorders is very well done in every way. Blood-transfusion techniques and theoretical discussion of blood-groups occupy about a third of the book, and these sections are also capably done. In the colour plates nuclear detail is obscure, and in the copy we received neither Cabot rings nor basophilic stippling of red cells had reproduced at all. There is a short bibliography which includes reference to two of the useful *British Medical Bulletins*, but not to any atlas of blood and bone-marrow cells. This book should certainly be considered by any technician studying for the I.M.L.T. examination and it is a useful reference book for the library in the hæmatology department.

Fellowship of Surgeons

A History of the American College of Surgeons. LOYAL DAVIS, M.D., F.A.C.S. Springfield, Ill.: Charles C. Thomas. 1960. Pp. 523. 84*s*.

AT the beginning of this century the United States was, as Garrison put it, " a paradise for quacks ". Legislation, which

should have covered certain aspects of its life, had not kept pace with the rapid growth of the nation, and the status of physicians and surgeons had notably suffered. The licensing of doctors had been enforced for some fifty years, but it was a function of State Governments, and the standards they required varied enormously up and down the country. There were, in 1907, more medical schools in the U.S.A. than in all the other countries of the world: but many were privately owned, and of the variety which awarded diplomas to "graduates" who might never have felt a patient's pulse. Once licensed, any doctor could style himself a surgeon, and might practise as such without further training.

In an effort to raise the standing of the profession, a Chicago gynæcologist, Dr. Frank Martin, founded, in 1905, a journal which was produced on novel and ambitious lines. So successful was this publication, *Surgery, Gynecology, and Obstetrics*, that five years later its editors were able to organise a fortnight's convention in Chicago. The opportunity it afforded of seeing operators like Ochsner and Murphy at work made this function extremely popular, and a series of similar gatherings followed. Martin realised the necessity, before the meetings became too unwieldy, of restricting attendance at them. From his clinical congress, with a selected membership, evolved very quickly the American College of Surgeons, which imposed stringent requirements in the way of training and conduct upon all who aspired to join it.

The College was, from its inception, modelled upon another already a hundred years old—the Royal College of Surgeons of England—and it is interesting to note common features in the history of both institutions. Just as Wakley and his supporters were fearful of the dictatorial powers that might accrue to "the diploma warehouse in Lincoln's Inn Fields", so some of the State medical societies attacked the new College, and poured scorn on those who applied for, or were granted, the privilege of adding the suffix F.A.C.S. to their names ("American Surgical Society" and even less elegant alternative titles were suggested). Yet it was also confronted by some difficulties which find no parallel in the English records. The election of coloured surgeons was one such issue, and the widespread practice of fee-splitting was another. Not until the late 1930s was the colour question finally resolved, when it was laid down that only professional and ethical considerations should influence the election of a fellow. And the struggle against the evils of dichotomy runs as a recurring theme through the whole history of the organisation.

Dr. Loyal Davis, himself a distinguished surgeon and an eminent member of the board of regents of the College, has here provided a detailed account of its inception and growth. The names of those men with which he is principally concerned —men such as Murphy, Evarts Graham, and Matas—are internationally famous, and the book is assured of many interested readers in this country as well as in his own.

Bartje, My Son

NEL VAN HOUTEN. London: Hodder & Stoughton. 1960. Pp. 80. 10*s*. 6*d*.

THE structure of modern society and the speed of modern life make it increasingly hard to care for mentally defective children at home. Yet the tendency of some parents of these handicapped children to "shirk their responsibilities" has often been deprecated by authorites who emphasise the importance to these children of family life and mothering. Even fewer people have tried to show how these children can actually enrich the lives of those who care for them.

In this book Mrs. van Houten describes her personal experiences with her son. After an attack of encephalitis at the age of thirteen months, Bartje was not only mentally handicapped but also antisocial, aggressive, and bad-tempered. After reading this book one can have no doubt that Mrs. van Houten and her husband are doing all they can to "lead Bartje to his right place in life, so that he will become a worthy citizen and a good man". She describes simply and without malice the shortcomings of much of the medical advice and treatment that she encountered. She and Bartje have both benefited enormously from the anthroposophical approach to mental handicap found in the Rudolf Steiner schools. The book is charmingly illustrated by photographs of Bartje's own paintings, which would do credit to any child of his age. One of the most interesting features of the book is the description of Bartje's relationship with an unconventional painter, who gave him lessons and was the first person to make real contact with the child.

Mrs. van Houten writes: "Bartje has certainly not wrecked our lives. Amazingly enough he has brought us closer together, because we had to forget about ourselves, I think". Her book will be of interest to everyone concerned with mentally handicapped children.

The History of Bacteriology

The late WILLIAM BULLOCH, M.D., F.R.S., emeritus professor of bacteriology in the University of London. Heath Clark Lectures. First published 1938. London: Oxford University Press. 1960. Pp. 422. 30*s*.

IN 1930, Professor Bulloch wrote the chapter on the history of bacteriology for the Medical Research Council's *System of Bacteriology*. This classic firmly established and gained wide recognition for Bulloch's reputation as the greatest authority of his day on the history of bacteriology. In 1937, when he delivered the Heath Clark lecture in the London School of Hygiene and Tropical Medicine, Bulloch added a good deal to what he had already written in the *System of Bacteriology* and he supplied also a bibliography of 66 pages giving references to nearly 1000 works, and a biographical section of 60 pages giving short accounts of some 350 bacteriologists. The result was this scholarly book, whose reprinting is very welcome. As Bulloch himself remarked, it is curious that so little has been written on the history of bacteriology in contrast to the vast and growing proportions of the science and its inescapable applications to daily life and medical practice. Indeed, before Bulloch's own contributions, we have to go back to Loffler's *Vorlesungen* published in 1887, which itself was incomplete because the promised second half never appeared. The eleven chapters of Bulloch's work, critical, illuminating, and occasionally amusing, traverse the ground from ancient doctrines of contagion to the 1937 views on immunity. Unquestionably, this is a book for every bacteriologist.

Design of Documents

LANCELOT HOGBEN, F.R.S., K. W. CROSS, PH.D. London: Macdonald & Evans. 1960. Pp. 88. 35*s*.

THIS book is an introduction to the design of punched cards suitable for storing medical records. The information stored includes signs and symptoms as well as items such as sex, age, and occupation. The coding system used in the Birmingham teaching hospitals for these items and others relating to laboratory investigations and therapeutic agents is detailed. While the system may be useful to medical recordists, the extensive use of over-punching reduces its general applicability. The records, it seems, are designed mainly to meet the requirements of simple sorting and tabulating, though certain quantitative items, such as anthropometric measurements, appear in the record sheet. The use of electronic, general-purpose, or data-processing computers is not discussed; nor is the design of the actual medical history records, perhaps because neither of the authors is a doctor. Those concerned with keeping records in hospitals will find the book useful.

Family Planning (Edinburgh: E. & S. Livingstone. 1960. Pp. 64. 3*s*. 6*d*.).—It is odd to reflect that no-one who buys a book with this title will expect it to be about planning a family, and of course it is not. But as a book of information and instruction in methods of avoiding unwanted and, to a less extent, securing desired pregnancy, this one by Dr. J. F. Robinson is quite admirable and well deserves the commendatory foreword by Sir Andrew Claye. It is illustrated by well-drawn diagrams and charts, has a list of approved contraceptive appliances and substances, and possesses an index.

THE LANCET
LONDON 20 AUGUST 1960

Acute Osteomyelitis

IMPROVING social conditions between the two wars so reduced the incidence of acute osteomyelitis that it became a relative rarity to the medical student of the 'thirties, and the antibiotic age has seen a dramatic fall in its case-mortality; yet it is still not uncommon and there is indeed an impression in some quarters that it is on the increase. WINTERS and CAHEN [1] have produced evidence that it is becoming more frequent in Louisiana, and, from South Africa, SHANDLING [2] reports 300 patients seen in seven years in Cape Town, where it has even proved necessary to maintain a special "osteitis ward" in the Children's Hospital. Only 50 of these patients were Europeans, but in this country it has been clear for some time that acute osteomyelitis is no longer a disease associated with poverty and malnutrition; the children of a well-to-do farming community will provide as high a proportion of patients as the poorest parts of the town.

Neither WINTERS and CAHEN nor SHANDLING give details of the duration of symptoms or treatment before admission to hospital, but certainly many of the patients had already been given penicillin. If one accepts that the treatment of osteomyelitis is essentially surgical it is easy to be critical of an often half-hearted exhibition of antibiotics, which not only tends to mask the local symptoms but may also result in a negative blood-culture and thus the loss of the earliest opportunity of identifying the organism involved and its sensitivity. But, in fairness to the general practitioner, surgeons must remember that when first presented to him the case may differ in no way from a score of others with a general infection of uncertain origin which his experience has shown will settle satisfactorily with the aid of penicillin. Furthermore it can be argued that the fatalities in osteomyelitis derive not from the bone infection but from the septicæmia which causes or at least accompanies it, and that the earlier antibiotic therapy is started the less will be the mortality. We shall never know in what proportion, if any, of such cases the osteomyelitis is completely aborted; but it seems likely that such a happy result never ensues once local symptoms and signs are manifest. In the South African series of 300 cases, 1 child died of malnutrition and 4 children of septicæmia, 3 of whom were infected with a staphylococcus sensitive to all antibiotics. There were no deaths in the 66 Louisiana patients. As usual, *Staphylococcus aureus* was responsible for the vast majority of infections in both series; but whereas only 57% of them were penicillin-sensitive in Louisiana, over 80% were penicillin-sensitive in the South African group.

WINTERS and CAHEN report the development of chronic osteomyelitis in 29% of their patients who were adequately followed up, a fact which they attribute to early but inadequate antibiotic treatment. It is apparent, however, that their patients were treated very conservatively, operation being reserved for those not responding favourably, and comparison with SHANDLING's results points clearly to the benefits of early operation. SHANDLING's best results unquestionably followed incision and drilling of the bone, and, rather surprisingly, were better still when the wound was drained. Drainage is popular with few orthopædic surgeons in this country, most of whom have found that after all pus has been removed and the metaphysis adequately drilled the wound can safely be sutured with every hope of primary healing without secondary infection. Adequate immobilisation of the affected part is important but is often forgotten: it adds greatly to the comfort of the patient and to the prospects of cure. In agreement with many authors, WINTERS and CAHEN and SHANDLING consider it wise to start treatment, immediately a blood-culture has been taken, with penicillin combined with one of the broad-spectrum antibiotics.

Both reports comment on the diagnostic difficulties of osteomyelitis of the femoral neck and the tragic results which may result at this site. Infection in this region is almost always accompanied by some sympathetic effusion into the hip-joint, and the patient often presents as an acute arthritis of the hip-joint rather than a bone infection. Primary suppurative arthritis of the hip-joint in older children is, however, a very rare disease, and there is much to be said for a policy of drilling the femoral neck from below the greater trochanter as a primary diagnostic and therapeutic measure whenever opalescent fluid is aspirated from the hip-joint. Many cases of the so-called septic epiphysitis of infancy are the result of infection primarily in the femoral neck rather than in the hip-joint itself.

There can be little doubt that operation is indicated as soon as there is the least suspicion of local abscess formation, or indeed if local signs without definite evidence of pus formation do not settle within twelve to twenty-four hours of the start of adequate antibiotic therapy. Most surgeons will agree that very rarely indeed do they regret having operated, and much more often they are sorry they did not operate earlier. Whether or not pus is found, the metaphysis should be drilled; the presence of a subperiosteal abscess does not mean that the metaphysis has already decompressed itself. Pus will often well up under considerable tension from the drill hole under these circumstances. Similarly the absence of a subperiosteal abscess should not deter the surgeon from drilling the metaphysis. Even if pus is not found within the bone, no harm has been done; a negative exploration does less potential damage than no exploration at all. Acute osteomyelitis remains a surgical disease.

1. Winters, J. L., Cahen, I. *J. Bone Jt Surg.* 1960, **42A**, 691.
2. Shandling, B. *S. Afr. med. J.* 1960, **34**, 520.

Too Many Platelets

THROMBOCYTOPENIA, the hæmorrhagic disease associated with diminution of platelets in the blood, is known to most doctors. There is also a much less common condition in which the blood-platelets are greatly increased; and, oddly enough, this too is associated with excessive

bleeding. The first reported case of this disease is probably that described by EPSTEIN and GOEDEL [1] in 1934. OZER et al.[2] have recently published a list of 48 cases of this combination of thrombocythæmia and hæmorrhage, and they added 7 more; GUNZ [3] has given details of another 5; so some 60 cases have been reported in twenty-six years.

At once a classification difficulty arises. High platelet-counts are found in more than one blood disease (in chronic myeloid leukæmia, for example); so the question is: Is there a "primary hæmorrhagic thrombocythæmia", or is this part of some other disease? The question is not merely academic, because treatment should as a rule be directed at the primary disease and not only at the thrombocythæmia if this is secondary. OZER et al. enumerate a set of diagnostic points for a diagnosis of "primary" hæmorrhagic thrombocythæmia. These are: (*a*) a history of hæmorrhages, superficial or deep, sometimes with thrombosis as well; (*b*) the presence of a spleen, which is usually enlarged (this excludes cases arising after splenectomy); (*c*) red-blood-cell count not over 6 million per c.mm., hæmoglobin not over 18 g. per 100 ml., hæmatocrit not over 54%, and white-blood-cell count not over 50,000 per c.mm (these points are to exclude cases of polycythæmia vera), and platelet-count persistently over 800,000 per c.mm.; (*d*) hyperplasia of all marrow elements with megakaryocytes prominently affected, platelet masses present, and increase of eosinophil and sometimes basophil leucocytes; (*e*) absence of leukæmic type of tissue infiltration. When these criteria are applied only 21 of the 48 cases considered by OZER et al. qualify as "primary". Even when all these criteria are met, another blood disease may appear. Of the patients described by OZER et al. 1 died of acute myeloblastic leukæmia three years after primary hæmorrhagic thrombocythæmia was diagnosed, and similar occurrences have been recorded by others. OZER et al. therefore think that hæmorrhagic thrombocythæmia must be one aspect of the myeloproliferative syndrome adumbrated by DAMESHEK [4]; but all the same they suggest that the concept of primary hæmorrhagic thrombocythæmia is "useful for the proper management of the patient". GUNZ reaches much the same conclusion, but he prefers to avoid the term "primary" altogether; "hæmorrhagic thrombocythæmia", he says, "should itself be regarded as one form, or probably one phase of a multifaceted myeloproliferative disorder, rather than a distinct entity". In practice this means that it is worth recognising and treating hæmorrhagic thrombocythæmia as an entity distinct from other blood diseases, but always remembering that another of the myeloproliferative conditions may appear later and change the course of the disease.

Consideration of the reported cases shows quite a distinct clinical picture. This is most often a disease of late middle age with a slight preponderance in females; the mean age of GUNZ's 50 reported patients was 51 years, but 30 of them were older than 50. The commonest symptom is bleeding, particularly gastrointestinal bleeding and from other mucous membranes. Minor trauma, removal of teeth, and surgical operations are liable to cause long-continued and excessive bleeding. Spontaneous bruising is common, and sometimes very large hæmatomas have formed after insignificant injuries. Thromboembolic symptoms are relatively infrequent, but thrombosis of various arteries and veins has been recorded. Enlargement of the spleen and the liver is common, but lymph-glands are rarely involved. Anæmia from blood-loss is usual, but sometimes there is slight erythrocytosis. The white-blood-cell count is nearly always raised; the cells are mostly neutrophil polymorphs, but some eosinophils, basophils, and myelocytes are often found.

The most puzzling feature of this syndrome is the bleeding, which is apparently paradoxical in the presence of platelet-counts of the order of 1–14 million per c.mm. There have been several detailed studies of the coagulation mechanism in these patients, but the results are somewhat contradictory. There does seem to be a definite but qualitative link between high platelet-counts and tendency to bleed (i.e., if a patient's platelets are reduced he is less likely to bleed); but there is no evidence that a patient with 3 million platelets is more liable to bleed than one with 2 million platelets per c.mm. The only definite abnormalities have been found in the thromboplastin-generation test when the patient's platelets are used in the test. The most usual finding is that thromboplastin generation is reduced when the patient's platelets are used at the same concentration as in vivo (i.e., at 1–14 million per c.mm.); but when the patient's platelets are diluted and used at the normal concentration of 250,000 per c.mm., thromboplastin generation is normal. Such a finding suggests that an antithromboplastic factor is present and active at these high platelet levels. But these findings are inconstant too: SOULIER et al.[5] found that sometimes thromboplastin generation was normal or subnormal at in-vivo platelet concentrations and was simply reduced by dilution; GUNZ found similar variations in 4 of his patients. SPAET et al.[6] point out that in some patients the antithromboplastic effect is still present at normal platelet concentrations. Another abnormality found by HARDISTY and WOLFF [7] was diminution of plasma and serum serotonin (5-hydroxytryptamine); but this too was inconstant, and the level of serotonin was unrelated to the severity of bleeding. Yet another finding was that of GIMENO ALFOS et al.,[8] who estimated the life-span of platelets by labelling with di-isopropylfluorophosphonate; in 2 cases of hæmorrhagic thrombocythæmia the life-span was somewhat prolonged—e.g., $13\frac{1}{2}$ days compared with a normal maximum of 10 days. We still seem to be without any clear explanation of the bleeding tendency in hæmorrhagic thrombocythæmia, and these varying results may well denote that it is a syndrome with more than one cause.

Hæmorrhagic thrombocythæmia is a chronic dis-

1. Epstein, E., Goedel, A. *Virchows Arch.* 1934, **293**, 233.
2. Ozer, F. L., Truax, W. E., Miesch, D. C., Levin, W. P. *Amer. J. Med.* 1960, **28**, 807.
3. Gunz, F. W. *Blood*, 1960, **15**, 706.
4. Dameshek, W. *ibid.* 1951, **6**, 372.
5. Soulier, J-P., Alagille, D., Larrieu, M. J. *Sang*, 1957, **28**, 277.
6. Spaet, T. H., Bauer, S., Melamed, S. *Arch. intern. Med.* 1956, **98**, 377.
7. Hardisty, R. M., Wolff, H. H. *Brit. J. Hæmatol.* 1955, **1**, 390.
8. Gimeno Alfos, L., Field, E. O., Ledlie, E. M. *Lancet*, 1959, ii, 941.

order; but the patient's condition gradually deteriorates if he is untreated, and he dies eventually from hæmorrhage, sometimes into the central nervous system. Various remedies have been tested. All reports agree that splenectomy makes the condition worse. Since there is a megakaryocytic hyperplasia, and since hæmorrhages can be checked by reducing the platelet-count, it seems reasonable to apply the suppressive drugs used for leukæmia. The nitrogen mustards have not been successful, but there are several favourable reports on radioactive phosphorus. GUNZ successfully treated 2 of his patients with ^{32}P; and OZER et al. gave this drug to 3 of their patients, but in 1 of these acute myeloid leukæmia ensued. FOUNTAIN,[9] in this country, treated 2 patients with ^{32}P and reported good results. GUNZ used busulphan (' Myleran ') as an alternative to ^{32}P in 2 patients, and considered that the results were equally good so long as the drug was given continuously as in the treatment of chronic myeloid leukæmia. Treatment is definitely worth while and will control hæmorrhage. Therefore, when hæmorrhagic thrombocythæmia is diagnosed, treatment should be begun without delay.

Noisy Factories

SOME penalties of living in an industrial society are unavoidable; but at least we could reduce the noise. On our highways some motor-cycles and some cars emit an inexcusably loud noise—an offence which can be dealt with under existing legislation, and which would be more often if more of us insisted. On the road noise may be just a passing nuisance. In factories, on the other hand, it is more commonly an ever-present distraction; and sometimes it menaces hearing.

The engineer and the physicist who have set in motion so many waves of sound around us can also do much to smother, isolate, deflect, and mop up these waves. In factories, as the Department of Scientific and Industrial Research[10] has shown, such abatement is a complex and costly undertaking. In industry willingness to spend money is, perhaps understandably, difficult to generate without the promise of direct economic gain: an employer may question the advantage of spending thousands of pounds in reducing the noise level in a workshop from 95 to 80 decibels, even though those working there will be enabled to make themselves understood without shouting. Nor is there any pronounced drive for less noise from the representatives of labour. It is surprising how indifferent a man will be to the incessant rattle of machinery, to the high-pitched whine of a saw, or to the affront from a nearby pneumatic tool or panel-beater.

There is ample evidence that, in the susceptible, intense noise can produce gross loss of hearing—a severe physical handicap with important secondary effects on mental health. A given intensity of noise is more damaging when concentrated into a pure tone than when spread over a wide range of frequencies. The ability to hear high-frequency sound, especially around 4000 cycles per second, is more susceptible to damage than the ability to hear low-frequency sound. Hence a man may still understand the low-pitched voice of his foreman when he has begun to have difficulty in hearing his wife and children.

Occupational deafness is no longer associated only with boiler-makers, naval gunners, and those whose main interest for thirty years has been shooting pheasants. In many a workshop concerned with the manufacture of motorcars, ships, locomotives, aircraft, canned goods, textiles, and building and roadmaking materials, even shouted words can hardly be distinguished; and if one remains, beaten into silence, the ears will ring on emerging. This is warning enough that some loss of hearing will develop in some workers after years of exposure. But opportunities for informing those at risk are not easy to come by; and even many of those in whom hearing is already waning either are unaware of this or else deliberately mask the loss. Only by direct inquiry is the physician who suspects early deafness likely to learn that the patient is subjected to intense noise at work. Such a patient should be urged to change his job, just as a patient with an intractable occupational skin disorder is advised to seek a change.

Deafness of occupational origin should surely be prescribed for compensation under the Industrial Injuries Act. Its present exclusion from the schedule under this Act is hard to understand.

9. Fountain, J. R. *Brit. med. J.* 1958, ii, 126.
10. Factory Building Studies no. 6: Noise in Factories. H.M. Stationery Office. Pp. 26. 3s. 6d.

Annotations

REGIONAL PLAN FOR ACCIDENTS

To produce a practical scheme for the integration of existing hospitals into an accident service for a large corner of England is a formidable challenge. It should embrace all hospitals, from the smallest and most limited to the largest and most comprehensive. Such a scheme has been put " on paper " for the South East Metropolitan Regional Hospital Board in a report from their senior administrative medical officer, Dr. J. S. S. Fairley, and was accepted by them on July 27.[1] Much of it already exists, of course, in longstanding arrangements, and the rest is to be brought into operation as opportunity arises and as resources permit. It is based on a few simple but fundamental principles:

1. Existing hospitals are to be graded according to their facilities for dealing with accident cases. Accidents are to be directed not to the nearest hospital but to the nearest hospital of an appropriate grade.

2. Completely comprehensive regional centres are to be situated at five nuclei. These are group-I hospitals, and include the teaching schools at Guy's and King's College. They will take casualties from all major accidents (50 cases or more) in their section. They will take major injuries (ambulance cases) from their own area. They will take minor injuries (walking cases) from that part of their area to which they happen to be the nearest hospital.

3. About ten other hospitals (designated group-II hospitals) will take major injuries from their own area, and minor injuries from nearby.

4. The remainder of the hospitals (group III) will take minor injuries from that part of the area to which they happen to be nearest, and their casualty departments will be associated with

1. *Times*, July 28, 1960, p. 7.

the group-II hospitals ("accident centres"), by frequent liaison and exchange visiting. Major injuries will normally be routed straight past these hospitals, but the scheme accepts that many modifying factors may alter this arrangement in special circumstances (for instance, if a patient is moribund); and it is hoped that the service will be flexible enough for mobile teams from the centres to keep the peripheral service at a very high level of efficiency. The determination to do this is very evident from the report.

Much time will be needed before the whole scheme can come to fruition, and Dr. Fairley emphasises [1] that an attempt to improve the treatment of accident cases by coordination should not undermine the public's confidence in the present arrangements. Though other areas are already working schemes based on similar principles—Windsor [2] is an example—the South East Metropolitan Region's is one of the largest. It stretches from London Bridge to the mouth of the Thames, and round the coast as far as Brighton, and covers all between. Its coordinated service is likely (as *The Times* says) "to be a model for the rest of the country". The rest of the country will certainly watch its progress with great interest.

ALCOHOLISM

WHEN, five years ago, the Swedes repealed their forty-year-old system of rationing alcoholic drinks, there followed the expected rise of alcohol consumption, gradually brought to a halt by increasing the excise duty. But abuse of alcohol, drunkenness convictions, and drinking by the young still present Sweden with a serious problem, which the State, with the support of an active enlightened temperance movement, is tackling by a well-organised programme of legislation, education, and research.

Rather than rely exclusively on legislation, as formerly, many State-encouraged programmes of the past fifteen years have included campaigns for educating the public, organising research, and providing facilities for treatment and reablement, as Archer Tongue told the 500 delegates from over 40 countries who went to Stockholm on July 31 to Aug. 5 for the 26th International Congress on Alcohol and Alcoholism. Such plans have been adopted in North America and some Latin American States, by France, the Netherlands, Switzerland, Yugoslavia, Russia, Poland, and Czechoslovakia. This approach is apparent in the recent grant of 1 million dollars by the U.S. Public Health Service to a United States and Canadian commission which will study everything that may contribute to the understanding and relief of alcoholism. The power of such State campaigns is reflected in the fact that France, for the first time since the war, has halted the steadily upward trend of alcohol consumption and deaths from alcoholism and cirrhosis, largely, it seems, because of the intensive and courageous anti-alcohol campaign of the French Government. State activity does not, however, remove the need for voluntary bodies. Apart from Alcoholics Anonymous, the best example is the American National Council on Alcoholism. Its national organisation and 60 local affiliations use the Press, radio, television, films, and a speakers' bureau to spread information and remove the stigma from alcoholism.

The importance of well-planned and controlled research was emphasised throughout the Stockholm conference. Prof. Heiki Waris, of Finland, illustrated how research findings influenced the formation of a national policy towards alcohol. Examples of research activities that the conference discussed were the work on the metabolism and action of alcohol at the Karolinska Institute, under Prof. L. Goldberg; the importance of "rum fits" and of delirium tremens as alcohol withdrawal symptoms, described by Dr. A. Wikler, of the U.S. Public Health Service; and the effects of even small doses of alcohol in impairing judgment and performance, as demonstrated by Prof. G. C. Drew (London).

No surprises emerged in the discussions on treatment and reablement. Tranquillisers, disulfiram, and group psychotherapy enjoy world-wide popularity. Slightly differing from the prevalent view of the alcoholic as a sick person, the Russian delegates viewed alcoholism as a sickness for which the patient must bear some measure of responsibility. The Russians, Poles, Hungarians, and Czechs took a large part in the proceedings, particularly in the showing of educational films about the risks of excessive alcohol consumption.

The final reviews from the five sections of the congress pointed to the need for international reports of alcohol consumption and for heavy taxation of alcohol. State monopoly of (at least) spirits would be an advantage. When the congress ended no spectacular drug had emerged to take the place of slow painstaking effort. But there was evidence of gradual steady progress and of cautious optimism. It seems that in Britain treatment and rehabilitation techniques in the few special public and private centres are as good as anywhere in the world. Alcoholism seems to be a much less urgent matter here than in many other countries, but that hardly justifies the lack of attention it receives from the Government compared with the ambitious schemes developed by even small nations such as the Dutch and the Swiss.

SICKNESS ABSENCE AMONG HOSPITAL NURSES

DESPITE the modern passion for record-keeping and the parkinsonian increase in hospital clerical staffs, there is surprisingly little information about morbidity among hospital nurses and the influence of such factors as marriage, age, sex, and residence in hospital on sickness-rates. This question has been approached by Barr,[1] who examined all the absences from duty for the year ended March 31, 1957, of nurses in the hospitals of the United Oxford Hospitals and the Oxford Regional Hospital Board.

The nursing staff consisted of 732 males and 5550 females in 103 hospitals with about 15,000 beds. Four categories of nurses were studied separately—namely, trained nurses, student nurses, nursing assistants in mental hospitals, and a miscellaneous group consisting of enrolled assistant nurses, nursing auxiliaries, and other nursing staff. Information about absence for sickness was supplied by the matrons of the hospitals. The indices of sickness used were two: (1) the "inception-rate" (i.e., the number of spells of sickness which start during a defined period divided by the average number of persons exposed to risk during that period, though in this investigation the average number does not seem to have been ascertained; and (2) the "average duration of a spell".

28 diagnostic groups were used for classification, and a 29th for conditions which did not fit neatly into any of these groups. Absences due to sickness—numbering 5309—formed 85·2% of absences from all causes. The total number of days lost through sickness was 68,536.

2. Arden, G. P., Herschell, W., Maudsley, R. H. *Postgrad. Med. J.* 1960, **36**, 376.

1. Barr, A. *Brit. J. prev. soc. Med.* 1960, **14**, 89.

Sickness absence was greater among students than among trained staff: for example, only 38% of the female students had no spells of sickness during the year, compared with 57% of the trained staff. Sickness absence was greater among non-resident than resident staff; and this difference was particularly great among the younger student nurses. Not unexpectedly the common cold was the commonest cause of absence.

The inception-rate for female nurses for all illnesses combined tended to fall with age after 20 years, but the average duration of absence tended to increase with age. The inception-rate did not vary between hospitals more than would be expected from the difference in composition of the staff. On the other hand the average duration of absence varied between one hospital and another.

The facts are fairly clear, but the conclusions to be drawn are less certain. Barr suggests that residential accommodation should be provided for young student nurses, but one would first like to be certain that the resident student nurses received care equivalent to that received by their non-resident counterparts in their spells of morbidity. Possibly the resident nurse should have been absent, but for some reason remained on duty.

Barr makes a plea for further research into the medical and administrative uses of sickness-absence statistics in hospitals, and would like to see all sickness absences for hospital staff periodically recorded on a standard form. Some of us are a little suspicious about records collected in this way, though we should all support an appeal for more information about the causes and prevention of morbidity among nurses.

SURVEYS OF STAPHYLOCOCCI

Johnson et al.[1] describe a survey of the prevalence of *Staphylococcus aureus* among 2164 patients seen by doctors in general practices in nineteen different localities throughout Australia. The patients all had skin or subcutaneous infections suspected of being due to *Staph. aureus*, which was in fact isolated from the lesions of 1657 of the patients. Nasal swabs were also taken from all patients; but *Staph. aureus* was isolated from only 34·9%, and Johnson et al. conclude that "skin carriage may be more important than nasal carriage in perpetuating the lesions". The nasal carriage varied, however, with the climate; the rate was 24% in tropical and subtropical areas in North Australia, compared with 43·8% in more temperate regions.

Analysis of antibiotic sensitivity of the staphylococci isolated showed that as many as 64% of those isolated from lesions and 56·7% of the nasal strains were resistant to penicillin. This high figure was partly attributable to the fact that 46·6% of the strains from lesions and 35% of those from nasal carriers were phage-type 80/81. The high prevalence of type 80 and related strains was apparent in all localities and in all age-groups. Limited observations suggested that in some localities some of the infections with these strains had been acquired in hospitals; but in other places the strains appeared to be widespread in the general community. Only a few strains were resistant to antibiotics other than penicillin.

Staphylococci of phage-type 80 were first detected in Australia in 1953, and in the following year strains of this type were responsible for 19 out of 24 outbreaks of neonatal staphylococcal infection in hospitals throughout Australia[2]; they were considered by Rountree and Freeman[2] to be of enhanced virulence. In March, 1955, a strain of this type turned up in a hospital in Southampton,[3] where it was responsible for outbreaks of infection of unusual severity in both maternity and surgical wards. Since then the distribution of staphylococci of phage-type 80 has become world-wide, and by 1957 they had been identified in more than forty epidemics.[4] Strains of this type now appear to dominate the scene throughout Australia in and out of hospital.

Recent surveys in England do not suggest anything like so high a prevalence of penicillin-resistant or phage-type 80 staphylococci. McDonald et al.[5] found that 42% of 1858 recruits to the Royal Air Force carried *Staph. aureus* in the nose, but only 14% of the strains were resistant to penicillin; and, excluding those who had lately been in hospital, less than 20% of the strains belonged to any of the phage-types (including 80) common in hospital outbreaks in Britain.[5] In comparing this study with that in Australia, we must remember that the Australian workers were concerned not with the healthy but with a group of patients specifically selected because they had staphylococcal infection.

Another recent survey comes from Helsinki, where Mäkelä took nasal swabs from 699 healthy adults and 597 healthy children.[6] Of the adults 42% carried *Staph. aureus*; 30% of the strains isolated were resistant to penicillin and 2% to tetracycline. The total carriage-rate of the children was 60%, but the prevalence of antibiotic-resistant strains varied with age. Thus the percentage of strains resistant to penicillin and tetracycline were: 4–15 years, 37 and 5·8%; 1–3 years, 80 and 31%; and under 1 year 94 and 39%. The strains isolated from infants reflected those in maternity hospitals.

Of 667 members of the staff of 8 hospitals in Helsinki about half were persistent carriers and another quarter occasional carriers; 70% of the strains isolated were resistant to penicillin, 23% to tetracycline, and 6% to chloramphenicol. More than 90% of the strains resistant to penicillin, streptomycin, and tetracycline belonged to 5 (out of a total of 31) phage-types, one of which was type 80. From not very clearly presented evidence in relation to material from infections, Mäkelä concludes that strains of phage-type 80 and 3C/55/71 were of higher than average virulence.

ANOXIA IN THE NEWBORN

FROM the moment when the healthy neonate takes his first gasp and large pressure swings occur in the thoracic cavity, the alveoli expand progressively. This process is aided by the erectile effect of the filling of the pulmonary capillaries[7]; and the resulting increased return of blood to the left auricle closes the foramen ovale and may reverse blood-flow in the ductus arteriosus, thus increasing oxygenation of the blood still further.[8] The steadily rising oxygen concentration in the blood initiates rhythmical activity in the respiratory centre and produces functional closure of the ductus arteriosus. This sensitive balance can be upset by many factors. Antecedent fœtal anoxia, raised

1. Johnson, A., Rountree, P. M., Smith, K., Stanley, N. F., Anderson, K. *Spec. Rep. Ser. nat. Hlth med. Res. Coun., Canberra*, 1960, no. 10.
2. Rountree, P. M., Freeman, B. M. *Med. J. Aust.* 1955, ii, 157.
3. Duthie, E. S. See *Lancet*, 1957, i, 93.
4. Schaffer, T. E., Sylvester, R. F., Baldwin, J. N., Rheins, M. S. *Amer. J. publ. Hlth*, 1957, **47**, 990.
5. McDonald, J. C., Miller, D. L., Jevons, M. P., Williams, R. E. O. *Proc. R. Soc. Med.* 1960, **53**, 255.
6. Mäkelä, P. *Ann. Med. exp. Fenn.* 1960, **38**, suppl. no. 1.
7. Bonham Carter, R. E. *Lancet*, 1957, i, 1292.
8. Born, G. V. R., Dawes, G. S., Mott, J. C., Widdicombe, J. G. *Cold. Spr. Harb. Symp. quant. Biol.* 1954, **19**, 102.

intracranial tension from traumatic delivery, and the depressant effect of drugs disturb both respiration and the peripheral circulation,[9] which at this time is largely confined to the central part of the body by reason of the high peripheral resistance and the elasticity of the large arteries. Owing to these factors, to the rapid heart-rate, and to the small stroke-volume, the circulatory system can adapt itself little to blood-loss or shock.[10]

About two-thirds of deaths immediately before birth are due to anoxia, which commonly results from interference with the placental circulation or inexpert anæsthesia.[11] Of those fœtuses which survive the " valley of the shadow of birth " handicapped by such anoxia, many can be saved. The first necessity is to clear the airway and then the stomach by suction with the infant in the head-down position; and thereafter the infant should be propped up to encourage descent of the diaphragm, since at this stage respiration is largely diaphragmatic.[12] Oxygen is then administered; but, if no improvement occurs, tracheal intubation should be carried out, applying suction first and then positive-pressure respiration.[9] The positive phase of such respiration should be short and should not exceed 35 cm. water pressure; though this may not inflate the alveoli, it fills the bronchi with an oxygen-rich mixture and may initiate respiration. Where facilities for such measures are lacking, mouth-to-mouth insufflation or artificial respiration by an improvised Eve's rocking method can be undertaken. Macroscopic damage to the lungs in the newborn has been demonstrated at pressures exceeding 70 cm. water, and traumatic pneumothorax and mediastinal or interstitial emphysema may develop if positive pressure is not carefully controlled. Accordingly augmented respiration by means of machines triggered by the child's own efforts have real advantages.[9]

THE UNCOOPERATIVE TUBERCULOUS PATIENT

WITH the development of effective treatment for tuberculosis, much of the fear and stigma once attached to this disease has gone. Intensified case-finding schemes are steadily reducing the infector pool by the discovery of unsuspected disseminators of tubercle bacilli, who become more important as their numbers decrease. As a rule, treatment is readily accepted. Occasionally, however, every attempt at cooperation fails, and treatment is persistently refused.

Lethal bacteria, like lethal weapons, should not be discharged in public places. It can be argued that the person who knowingly and wilfully continues to threaten the public weal in this way should be compelled to submit to treatment or at least isolation. But any compulsion which restricts personal freedom requires the clearest justification; and in some countries—Austria, for example —it has apparently been decided that there is no such justification in the case of the tuberculous, however infectious they may be. Certainly if there are to be powers to enforce treatment or isolation, their exercise must be rigorously controlled.

In this country, as regards infectious conditions other than tuberculous, under section 169 of the Public Health Act of 1936 a justice of the peace (acting if he chooses *ex parte*) may order removal to hospital. In respiratory tuberculosis, an order for compulsory admission to hospital can be made (under section 172) only by a court of summary jurisdiction. The court must be satisfied that the patient is infectious, that proper precautions cannot be or are not being taken, that serious risk thereby exists to others, and that a specified hospital is willing to receive the patient. Due notice of the application must be given to the patient, who may be legally represented. The section does not apply to London or to Scotland.

Davies and Howell [1] report seven cases in which compulsory admission orders were obtained under section 172. In one case, action was taken more to save the patient's life than to protect others; the remaining six were all persistently uncooperative. Davies and Howell found to their surprise that after admission these patients became fully cooperative. In all seven the outcome of treatment was good, and those discharged from hospital are attending chest clinics regularly for follow-up.

Griffith [2 3] described an unsuccessful attempt to detain a tuberculous person in hospital after a court order had been obtained. Although this case is perhaps exceptional, it illustrates very clearly how a determined person may make a farce of the procedure. The order may be served only by the individual (usually a medical officer of health) named by the court, and it applies only to the hospital named in the order. A person who evades service of the order by absconding cannot apparently be sought out and detained by the police pending the arrival of the nominated person. Once admitted, the patient is, it seems, under no compulsion to remain in hospital or to cooperate in any way. Absconding from hospital or creating a nuisance in hospital when under order does not apparently amount to wilful obstruction in the legal sense. Even if it did, the only penalty (under section 288 of the Act) is a fine. Griffith, with some truth, describes an order under section 172 as no more than a piece of legal bluff; but, as Davies and Howell have shown, it can be an extremely useful and effective bluff.

At a meeting of the British Tuberculosis Association, Hamilton [4] reported a series of forty compulsory admissions in New South Wales. These were generally regarded as fully justifiable and created no political or other public opposition. The penalty for non-compliance in this State was £20. In Canada it is apparently the custom to set aside a special ward, devoid of amenities and christened " the cooler ", for such recalcitrant patients. In Ireland, under the Infectious Diseases Regulations of 1948 and the Health Act of 1947, a chief medical officer can compel suspected disseminators of infection to submit themselves to examination (including the collection of blood or other specimens). Force may, if necessary, be used to implement a compulsory admission order. Failure to comply, wilful misbehaviour, or attempt to escape carries liability to a fine of up to £50, three months' imprisonment, or both. Flynn,[5] reporting three compulsory admissions in Westmeath, produced evidence of a considerable subsequent decrease in uncooperative patients; and the number of new patients afterwards referred for investigation did not suggest that the disease was being driven underground.

In tuberculosis, perhaps more than in any other disease, cooperation between patient and doctor is vital to success. Compulsion is distasteful and must be a last resort; but if section 172 is to remain it should be made universally applicable and capable of enforcement.

9. Donald, I. *Brit. J. Anæsth.* 1960, **32**, 106.
10. Graham, G. R. *ibid.* p. 97.
11. Butler, N. R. See *ibid.* p. 102.
12. Karlberg, P. *J. Pediat.* 1960, **56**, 585.

1. Davies, J. B. M., Howell, F. R. *Med. Offr*, 1960, **103**, 281.
2. Griffith, A. H. *ibid.* 1959, **101**, 246.
3. Griffith, A. H. *ibid.* 1960, **103**, 310.
4. Annual meeting, British Tuberculosis Association, Oxford, July 8, 1960.
5. Flynn, M. P. *ibid.*

Special Articles

A CLINICAL SURVEY OF BLOOD-TRANSFUSION

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OVER the past few years there has been a steady increase in the demand for blood (fig. 1). In view of the frequent shortages this has caused, a survey of current transfusion practice was made in a London teaching hospital. Its purpose was to find out whether this increased demand for blood must be met by an increased supply, or whether it could be met by more discriminating use of the present supply.

The problem at the transfusion centre is to synchronise the varying availability of blood with the varying demand. In each year the periods when it is possible to collect most blood do not coincide with the times of greatest demand, and there is no means of stockpiling what is collected. If the supply drawn from donors were steady there would be enough to meet all needs in the foreseeable future. But as there is at present no way of avoiding seasonal shortages due to the illness or holidays of donors, it is logical to try to prevent the repeated crises by cutting down the demand.

The economic aspect of transfusion should also be considered, though the cost is much reduced by the system of voluntary donation. In this region the collection, testing, and delivery of blood to the hospital costs 21*s*. 6*d*. a bottle (420 ml.). Salaries and equipment for laboratory staff bring the price up to 40*s*. In comparison, the cost of dextran to the hospital is 19*s*. a bottle.

The Investigation

Four months before the survey started, a letter was sent by the laboratory staff to all clinicians urging every reasonable economy in the use of blood. Transfusion practice as recorded in the survey was no doubt affected both by this letter and by the knowledge that the reason for each transfusion was being recorded.

The main supply of blood comes from the South London Transfusion Centre at Sutton, the stock in the hospital being made up weekly, when possible, to a total of 100 bottles. At times of acute shortage, or when fresh blood is required for special purposes, it is taken from Red Cross or internal donors at the hospital. The survey accounted for every bottle of blood, dextran, and plasma used over a four-month period.

The hospital has 610 " acute " beds (280 surgical, 240 medical, and 90 obstetrical and gynæcological). The number of admissions in the four months was 4485 compared with 4300 in the corresponding period of the previous year. The number of operations performed was 1732, divided arbitrarily into three categories according to severity:

1. Minor surgery (excluding biopsy and endoscopy)	1081
2. Major surgery (cholecystectomy to pneumonectomy)	639
3. Œsophageal and aortic resections, pancreatectomy	12

For each patient who received blood, plasma, or dextran the following information was collected: (1) hæmoglobin (*a*) in outpatients, (*b*) before operation, and (*c*) after operation (if indicated); (2) diagnosis; (3) surgical operations and their severity; (4) operative blood-loss; (5) replacement therapy given; (6) person ordering transfusion; (7) reason for transfusion; and (8) preoperative iron therapy. It was hoped that from these data any obvious misuse of blood could be traced to its source, and that various views on supposed abuse could be confirmed or disproved.

The disposal of all bottles of blood was checked each day by one person. Other details were obtained from those looking after the patients and from the clinical notes.

AMOUNT OF BLOOD USED

During the four months 1112 bottles were given to 318 patients—namely, 975 bottles of blood (88%), 113 bottles of dextran (10%), and 24 bottles of plasma (2%). Of the blood-transfusions, 47% were ordered by consultants, 50% by registrars, and 3% by housemen.

The disposal of 1208 bottles of blood was reviewed:

975 bottles were used.
58 bottles were returned to the transfusion centre.
10 bottles were wasted.
45 bottles were untraced.
60 bottles were sent to other hospitals.
60 bottles remained at the end of the survey.

Excluding the 120 bottles in stock and sent elsewhere:

90% was given to patients	975
5% was returned to the centre	58
4% was mislaid	45
1% was wasted	10

(If only part of a bottle was used it was included among those given.)

The fact that 4% of the blood which was labelled was untraced demands explanation since it might suggest that the method of survey was inefficient. Among the reasons for this unsatisfactorily high figure are:

(1) Blood is sent to other hospitals in this group and elsewhere, and these transactions are not always recorded. (2) Individual bottles, after cross-matching, are taken as required from the bank without being " checked out " by the laboratory staff. (3) A daily count of all bottles in stock is not feasible unless the refrigerator can be opened from above. (4) After a bottle has been cross-matched two or three times, there is more difficulty in tracing the recipient. (5) To reduce the number of bottles untraced would have required a much more complex system of checking. (6) There was no evidence of unauthorised removal of blood, or of its being poured down the sink to conceal administrative inefficiency.

Of the blood given to patients 86% was given for surgical conditions (841 bottles) and 14% for medical conditions (134). (The 129 bottles [13%] given for hæmatemesis and melæna are included under surgical conditions.) Of the 975 bottles, 858 were supplied by the South London Transfusion Centre and 107 were taken from donors at the hospital. The latter were used for the following purposes:

Exchange transfusions	4
Hæmophilia	47
Heart-lung machine	11
Splenectomy (platelets)	12
To make up stock	16
Not used for special purpose and given routinely	17

10 bottles of blood were wasted (left out of refrigerator, 3; broken, 0; technical errors in laboratory, 5; contaminated, 2).

NECESSARY OR NOT?

In considering whether transfusions were clinically justified the following criteria were used:

1. Single-pint transfusions should not be given to adults.
2. Where anæmia is not due to acute blood-loss, it should

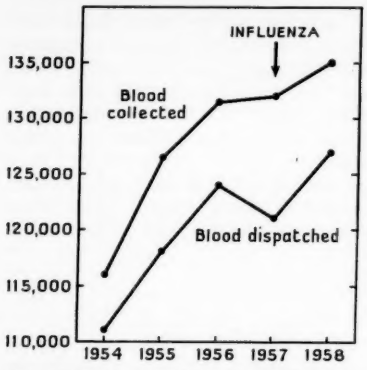

Fig. 1—Blood collected and dispatched by the South London Transfusion Centre.

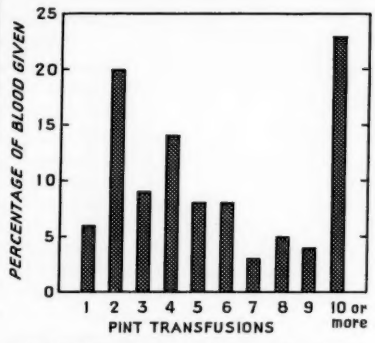

Fig. 2—Disposal of the blood used, giving the total amount received by each patient.

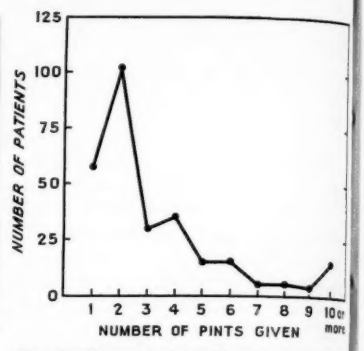

Fig. 3—Disposal of the blood used, giving the number of patients receiving small or large transfusions.

be treated by transfusion only if it will not respond to drugs.

3. Patients dying of incurable disease should receive blood only if anæmia is the cause of their symptoms, and if its correction will be followed by a period of enjoyable existence.

4. Preoperative transfusion is indicated by the urgency and not the expediency of the operation.

5. Massive acute blood-loss requires rapid and adequate replacement of red cells and plasma.

6. Moderate acute blood-loss does not require transfusion of red cells (as opposed to dextran or plasma) unless it is causing, or is likely to cause, significant anæmia.

7. Postoperative transfusion is indicated more by the extent of the residual pathology than by the presence of anæmia.

On the criteria given above, 64 bottles of blood were given unnecessarily, amounting to 6·5% of the blood used.

Single pint	16
"Medical" anæmia	3
Dying patients	4
Inadequate preparation for surgery	11
Moderate acute operative loss	6
Expectation of further loss	18
Postoperative anæmia	2
Postoperative collapse	4

44 patients received one-pint transfusions as sole replacement therapy. This represents 4·5% of the total amount of blood given. The disposal of these 44 bottles was:

Given to children	9
During major surgery in expectation of further loss	14
Misunderstanding between surgeon and anæsthetist	1*
Should have received 2 pints	3*
Acute collapse of unknown ætiology	1
Administration unjustified	16*

LARGE TRANSFUSIONS

15 patients received 10 or more pints of blood:

	No. of patients	*No. of pints*
Gastrectomy for hæmatemesis	5	(12, 15, 11, 10, 12)
Colectomy for carcinoma	1	(10)
Colectomy for ulcerative colitis	1	(10)
Aortic resection	2	(11, 14)
Pulmonary stenosis and atrial septal defect (on pump)	1	(13)
Following prostatectomy	2	(14, 14)
Carcinoma of bladder (biopsy only)	1	(11)
Dental extraction in hæmophiliac	1	(47)
Lymphosarcoma	1	(14)
	15	

* 20 pints—given as definitive replacement therapy—represent 2% of total blood usage.

PLASMA AND DEXTRAN

24 bottles of *plasma* were given to 10 patients:

After dextran, awaiting blood	2
Acute effusion of protein-rich fluid into peritoneal cavity	5
Chronic protein loss or depletion	3
Severe burns	0

113 bottles of *dextran* were given to 84 patients:

For choice	
As sole replacement therapy	29
Combined with blood	32
While awaiting blood	23

EFFECTS OF SURVEY

The fact that the survey was carried out by a clinician known to those who were interrogated prevented feelings of unjustified interference or resentment. The information was received without comment unless this was asked for.

Compared with the same period of the previous year, 200 fewer bottles of blood (or 16% less) were supplied by the transfusion centre during the four months of the survey (fig. 2). Probably, therefore, more rather than less blood would have been demanded and supplied if the inquiry had not been in progress. During the four months only 16 pints had to be drawn from donors at the hospital to replace depleted stock at times when the centre could not supply the necessary blood.

It was known that one-pint transfusions were under critical review, but examination of the records does not support the suggestion that two-pint transfusions were given instead of one-pint transfusions in order to avert criticism. During the survey there was no gross misuse of blood (fig. 3) but 6·5% could have been saved.

Discussion

Whereas twenty years ago blood-transfusion was a therapeutic event, it has now become commonplace; and at times it is administered or withheld with little consideration of the real need. Many will recall resistance to very necessary transfusions, while others will recall refusal to perform any major operation without giving a pint of blood. In traumatic surgery there is still reluctance to give enough blood sufficiently rapidly; and, in general, a lot of unnecessary small transfusions are given. Taking radical mastectomy as an example, those who always, or never, give blood are likely to be at fault. To withhold or give blood as a routine is a clear sign that further thought is necessary.

CRITERIA FOR TRANSFUSION

Single-pint Transfusions

These may be given in combination with dextran to restore blood-volume. During a major operation, such as mitral valvotomy, one pint is often administered in the reasonable expectation of sudden acute blood-loss.

It is the administration of one pint of blood by itself, on the ground that " he would be better with a pint ", that is hard to justify; for the arguments against it are formidable when the possible benefits and dangers are considered.

Using a pint bottle of ordinary stored blood, the blood-volume replacement is approximately 370 ml., or one-fourteenth of the normal blood-volume. In routine hospital use most of the blood given is nearing its expiry date, and about 20% of the corpuscles will disappear from the circulation in the first twenty-four hours. To raise the hæmoglobin level by 6% is a similarly unimpressive achievement and unlikely to affect postoperative progress. Unpublished data suggest that, judging by the subsequent hæmoglobin level, millilitre-for-millilitre, replacement of blood lost during gastrectomy is not advantageous compared with similar use of a blood-volume expander (Thorsén 1959).

On the other hand, the mortality has been estimated as one to every 1000–3000 transfusions (Guynn and Reynolds 1958). This estimate was based on figures from leading centres, and in hospitals as a whole the mortality may be higher. The incidence of virus hepatitis is one in every 200–500 transfusions (Hoxworth et al. 1959).

If blood is necessary it should be given in a therapeutic dose. To give less than this exposes the patient unjustifiably to the hazards of transfusion without apparent benefit.

(16 bottles given without justification during survey.)

Anæmia not due to Acute Blood-loss

Despite a hæmoglobin of 25%, a patient with a specific deficiency anæmia may walk up to the hospital. In such a case administration of iron or other drugs is the treatment of choice. Many chronically ill patients have a hæmoglobin which stabilises at about 60%. Transfusion will temporarily raise this but will inhibit endogenous red-cell production, and will be followed by return of the hæmoglobin to its previous level. In these two instances transfusion would be wasteful unless a surgical procedure was imminent.

(3 bottles given without justification during survey.)

Incurable Disease

The abuse of transfusion therapy in the dying is both unkind and wasteful. It does not seem to be generally appreciated that a hæmoglobin level of 40% or over is adequate for those who for other reasons are confined to bed or grossly restricted in their activity. Where patients are suffering great pain and other privations transfusion can only make them more acutely aware of their misery. It is misused in attempting to delude the patient or relations into thinking that something is being done, or to enable the patient to be discharged from hospital unless definite benefit is likely.

(4 bottles given without justification during survey.)

Preoperative Transfusion

Failure to order simple outpatient investigations and failure to initiate straightforward outpatient treatment is responsible for the admission of patients too anæmic for operation. Preoperative transfusion is unfortunately more convenient and cheaper than discharge of the patient on appropriate treatment, with subsequent delay in filling the vacant bed.

To say that major surgery cannot be undertaken if the hæmoglobin is below some arbitrary figure, such as 80%, is wrong. One should consider such factors as the average normal hæmoglobin for the patient's age and sex and the nature of the operation. A straightforward hysterectomy is not so severe as an abdominoperineal resection of the rectum.

In urgent cases gross anæmia (50%) must be corrected by transfusion, or transfusions—preferably two days before operation, if necessary using packed cells. There is no objection to the correction of moderate anæmia (70%) at operation.

The existence of chronic shock—a term used to describe the state of debilitated patients with recent weight-loss—is questionable (McMurray et al. 1956). It has been suggested that before operation these patients should be given 100 ml. of whole blood for every pound of weight-loss over the preceding two months (Guynn and Reynolds 1958). But, in view of plasma-volume expansion, which maintains the normal blood-volume despite depletion of red-cell mass, packed-cell transfusion seems more suitable than whole blood.

(11 bottles given without justification during survey.)

Massive Blood-loss

Acute losses are usually underestimated and replaced too slowly. A reasonable calculation can be made of blood-loss into the tissues in fractures and from open wounds (Grant and Reeve 1951, Clarke et al. 1955, Clarke 1959). Loss during operation can be measured accurately by weighing the swabs and by adding 25% to the weight for blood lost into the tissues and on towels and gowns (Cáceres and Wittembury 1959).

Overloading of the circulation is unlikely after major trauma if a reasonable estimate of blood-loss is made and if the patient's general condition and venous pressure are watched. The risk of causing further bleeding by adequate transfusion is theoretical, and slight, compared with the risk of under-transfusion.

The use of pressor agents such as noradrenaline is hazardous in shock. They may raise the blood-pressure and discourage adequate blood-volume replacement. If they are used for shock, caution, and some knowledge of recent work on irreversible shock, are advisable.

(No blood given unjustifiably during survey and no evidence of gross under-transfusion. Despite a policy of early operative intervention, 5 patients undergoing emergency gastrectomy required 10 or more pints of blood.)

Moderate Blood-loss

A loss of up to 600 ml. in the old or debilitated, or 1000 ml. in the healthy patient, can be called moderate. In the absence of anæmia, or expected continued blood-loss, blood replacement is not necessary. If the patient is collapsed the blood-volume requires adjustment, but there is not necessarily any need to increase the oxygen-carrying capacity of the blood. In these conditions dextran is the ideal means of replacement.

(6 bottles given without justification during survey.)

Postoperative Transfusion

As regards moderate anæmia, there is no evidence that

patients really " do better " and resist infection, or that wounds heal faster, with transfusion. The collection of sufficient evidence to decide this issue would be a daunting task. The presence of severe anæmia in addition to gross disease is a clear indication for blood. Patients with anæmia associated with fluid and electrolyte losses from high intestinal fistulæ or extensive chronic sepsis usually require transfusion.

(2 bottles given without justification during survey.)

ORDERING OF BLOOD TRANSFUSION

The preparation of surgical patients to ensure that they come to operation without significant anæmia and without blood-volume depletion due to loss of fluid and electrolyte is the responsibility of the surgeon. The replacement of loss during operation should be in the hands of the anæsthetist, whose views are in accord with those of the surgeon, and who should see that the blood-volume at the end of the operation is adequate. The anæsthetist knows the blood-loss at any particular time, and whether any lowering of the blood-pressure is due to this loss, to change of posture, or to the anæsthetic.

In the recovery room, or immediately after return to the ward, responsibility for further blood replacement should ideally be agreed between surgeon and anæsthetist. It is desirable that in the immediate postoperative period the anæsthetist should not confine his attention to the respiratory system.

The pathologist is not directly concerned with the clinical management of the surgical case, but his confidence and cooperation can be forfeited by misuse of the blood he has supplied and which may be very scarce—a fact perhaps known only to him.

Swab weighing is at present the only practical method of obtaining an accurate assessment of blood-loss. Major surgery, especially when considerable hæmorrhage is likely, should not be undertaken unless there are facilities for measuring blood-loss. Direct and repeated readings of the blood-volume can be obtained by means of radioactive isotopes, but their use is limited at present to a few centres (Albert et al. 1958).

DEXTRAN AND PLASMA

Some clinicians are suspicious of the effects of dextran and reluctant to use it for supportive therapy. It has been said to increase bleeding, and its fate in the body is stated to be uncertain. A brief summary of the facts should dispel these doubts.

There is no evidence that 500 ml. of dextran has any effect on the bleeding-time. 1000 ml. in normal humans, and equivalent doses in dogs, have sometimes been found to prolong bleeding-time (Carbone et al. 1954, Adelson et al. 1955); but using slightly less trauma, up to 1500 ml. has been given without altering it (Nittis et al. 1953). In the experiments showing increased bleeding-times the increase was not at the time when the plasma volume was greatest—i.e., immediately after the infusion (Carbone et al. 1954). Clinically there is overwhelming evidence that dextran is a safe and satisfactory blood-volume expander, and there is no reason to believe that, in moderate amounts, it increases bleeding (Artz et al. 1955).

There is no mystery about the fate of dextran. It is either excreted in the urine or metabolised. Some dextran is incorporated in the tissues but does not cause histological changes. Radioactive-carbon studies show that in dogs excretion from the body is complete in five weeks (Terry et al. 1953). Reactions to the dextran now in use are very uncommon, especially in patients whose blood-volume is depleted.

In concealed accidental hæmorrhage, where further dilution of fibrinogen and other clotting factors in the blood are undesirable (Barry et al. 1955), plasma or blood is preferable to dextran.

Under present storage conditions there is no indication for increased use of plasma. Its more frequent use may become desirable if the risk of serum hepatitis can be eliminated by keeping liquid plasma at room temperature for six months (Hoxworth et al. 1959).

Conclusions

1. Single-pint transfusions should not constitute more than 5% of the blood used in any hospital.

2. Before each pint of blood is given, two questions should be answered: (*a*) is it necessary? (*b*) is its purpose to restore blood-volume or to increase the oxygen-carrying capacity of the blood?

3. All routine dogma concerning transfusion should be abandoned and each case should be dealt with on its merits.

4. Increased use of dextran is desirable. Where a patient has lost blood during operation but is not otherwise anæmic a fair case can be made for giving one pint of dextran before blood.

5. Rule-of-thumb replacement is no longer acceptable. Accurate swab weighing and sensible estimation of non-operative loss are essential.

6. The principles of blood-transfusion should be understood, and policy agreed, between surgeon, physician, anæsthetist, and houseman.

7. Hæmoglobin should be estimated, and anæmia should be treated, in the outpatient department. Patients who do not require urgent operation should not be admitted until treatment of anæmia is known to have succeeded or failed.

8. Timely surgery will sometimes stop hæmorrhage, and during operation every care should be taken to prevent blood-loss.

9. Practice of these principles would save much blood and go far to obviate the present inconvenient shortages.

I wish to thank Dr. Gordon Wetherley-Mein, of the Louis Jenner Laboratory, for his help, and Dr. R. A. Zeitlin, of the South London Transfusion Centre, for his cooperation. I am also indebted to the laboratory technical staff, and to Miss P. Leicester for secretarial assistance.

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Occasional Survey

MEDICAL AND BIOLOGICAL ASPECTS OF FLUORIDATION

THE response to our recent review [1] illustrated how opposition to fluoridation has two main arguments: compulsory medication, irrespective of its efficacy, is repugnant; and insufficient is yet known about the chronic toxicity of fluorides. Moral scruples are always worthy of respect, especially when purely objective and unbiassed; but some of the arguments are hardly tenable. It is unlikely, for instance, that those who support fluoridation have no concern for children's teeth, but wish only to break down the fundamental principle of consent to treatment [2]; nor is it any more probable that the continued support from various public bodies for fluoridation projects in the United States, in spite of the publication of some adverse reports, is a mere face-saving manœuvre.[3] A far more cogent argument is that the effects of the long-term ingestion of low concentrations of fluorine are unknown, and will remain unknown unless experimentation is carried out on an impossibly large scale. The hypothesis that small amounts of fluoride are essential nutrients for the living cell does not receive universal support, particularly since the fluoride ion is a powerful anti-oxidase and can inhibit lipase at a concentration of 1 part in 5 million.[4] Even the proponents of fluoridation agree that it is of limited value after about 16 years of age, and it is argued that it is quite unjustifiable to expose the whole adult population to any possible risks of chronic fluoride intoxication. The ingenious proposal has been made that fluorides should be administered in school milk.[5] Unfortunately, few of the under-5s would benefit, and some workers believe that calcium may interfere with the absorption of fluoride. Fluorides usually occur naturally in water with a high calcium content, and the effects of fluoride ions may well be modified in soft water.[6] Burrowes [7] has pointed out that in a fairly high-fluoride area (3·5 parts per million (p.p.m.)), the most severe mottling was seen in the teeth of children who were tea-drinkers while it was much less in those whose main drink was milk.

Skeletal fluorosis may not be the only danger; new growths, in particular gastric carcinomas, are reported to be commoner in the areas where the water is naturally fluoridated. For example, in Utah County, Utah (about 0·5 p.p.m. fluoride), in the period 1955–57, new growths were given as the cause of 2·4% of all deaths; in the same period in Colorado Springs (2·5 p.p.m. fluoride), no less than 28·8% of all deaths were ascribed to them. The precise significance of these figures is uncertain because of the lack of information about a host of modifying factors, such as the age-distributions of the two populations. Again, in Lincolnshire, deaths from gastric carcinoma in Crowland, where the water is naturally fluoridated at 3·5 p. p. m., were more than twice as many over a 10-year period as in Donnington, where the water contains 0·5 p.p.m. of fluoride.[7] This might be accounted for by chance variations in the two populations, or it might be a " real " difference, but one not related to the water-supply. Such apparently inexplicable local differences have been observed elsewhere, both in this country [8] and in the Netherlands,[9] and could be due to some difference in the organic or trace-element content of the local soils. There is always a danger when evaluating statistics of indulging in post-hoc reasoning.[10] Both the opponents and supporters of fluoridation could claim that this fallacious method of reasoning has been used against them, but too much reliance must not be placed on sets of numerical data alone—assumptions must be tested against a background of sound clinical knowledge and experience.

The two extreme views on fluoridation are represented by the Ministry of Health who declare categorically [11] that there is no scientific evidence that fluoridation at a level of 1 p.p.m. has any deleterious effect on the health of either adults or children, and by the Pure Water Association [2] who consider that it is both unethical and unjustified to impose a general and permanent intake of a " well-known poison ".

Fluorine and Fluorides

Occurrence

Elemental fluorine is a highly reactive substance and does not occur free in Nature, but the fluorides, both simple and complex, are found almost universally. Many of them are only sparingly soluble in water, and their toxicity is related to their solubility and their degree of dissociation—hence, sodium fluoride is more toxic than the corresponding calcium salt.

Fluorides are always present in the atmosphere, even in areas well away from industry. The concentration may be as high as 48 parts per 100 million (Fort William, in Scotland, where large quantities of cryolite are handled), or as low as 0·02 part per 100 million (Utah County, Utah). A typical value for an American city is 15 parts per 100 million.[12]

The average concentration of fluorides in the earth's crust is 300 p.p.m. (with a range from 50–500 p.p.m.), although as much as 1200 p.p.m. may be present in some native ironstone. The fluoride content of coal lies between 0 and 175 p.p.m.[12] The amount absorbed by vegetation depends upon the solubility of the fluorides present in the soil, but is seldom below 0·10 p.p.m. or above 10 p.p.m. in the United States; a higher upper limit of 12 p.p.m. is quoted for this country. As much as 2000 p.p.m. have been found in plants growing in an area where ironstone was calcined, but such a concentration is exceptional.

The fluoride content of water is extremely variable, ranging from 0 p.p.m. in much of Australia to 53 p.p.m. in one part of South Africa. 1·0 p.p.m. appears to be the maximum amount found anywhere in Australia, and 0·24 p.p.m. is a usual value for South Africa. In Great Britain, the amount present may be anything from a trace to 4 p.p.m. (Maldon in Essex is unique in having a concentration of 6 p.p.m.).

Foods also vary widely in fluoride content. Some representative values are: fish 25·51 p.p.m. (mackerel), with an average of 9·4 p.p.m. for edible species; meat 1·06 p.p.m. (average), and potatoes 1·19 p.p.m. Tea contains an average of 53 p.p.m. by weight of fluoride, but some samples may contain as much as 399 p.p.m.[12] The fluoride content of milk lies between 0·09 and 0·35 p.p.m., and is not significantly changed by large variations in the amount of fluoride present in either animal feeding-stuffs or drinking water.[13]

The daily intake of fluoride is low. Figures quoted for Great

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Britain are about 1·8 mg. for men, 1·3 mg. for women, and 0·6 mg. for children. These figures include fluoride derived from drinking water, at an unspecified concentration, but one which would probably be about 0·5 p.p.m. The daily intake is probably less in the United States, as the American does not relish the Englishman's " nice cup of tea ".

Toxicity

Brun et al.[14] believed that a daily intake of 28 mg. of fluoride over many years was necessary to produce fluorosis, but later workers consider that this figure is too high and would place it at 20 mg. or somewhat less. A complicating factor is the long time-lag (some 10–20 years) between the ingestion of fluoride and the appearance of crippling osteosclerosis.

Brun observed that cryolite workers continued to excrete large quantities of fluoride in the urine for some years after exposure had ceased. These fluorides probably came from the breaking-down of pathological bone tissue, for the ex-miners showed less osteosclerosis than those actually at work. There are several environmental and physiological factors which influence the effects of fluorides. Discussing toxic dusts generally, Zangger[15] remarks that there is always more trouble in hot weather and in southern climates; this conclusion has been confirmed by experience in the United States. Species tolerance differs considerably, dairy cows being far more susceptible to skeletal fluorosis than poultry.[13] Tolerance may be decreased by infection, by increased energy demands, by changes in dietary factors, and by faulty nutrition. In addition, growth, lactation, and pregnancy appear to decrease tolerance, at least in animals.[16]

Recent official recommendations on the maximum permissible quantities of toxic dusts for chronic exposure allow up to 2·5 mg. of fluorides per cubic metre—about twice the permissible concentration for dicophane (D.D.T.). Gaseous fluorine is considered to be safe in concentrations up to 0·1 p.p.m., or 0·2 mg. per cubic metre.[17]

There appears to be a wide margin of safety in the amount of fluorine that can be handled by the human body. Differences in species tolerance have already been mentioned, so the results of animal experiments may not be directly applicable to human subjects. The maximum lethal dose (by intravenous infusion) is approximately 20 mg. per kg. for dogs and 23 mg. per kg. for mice. The oral lethal dose is 46 mg. per kg.[18]

Hodge[19] summarises the effects of fluorides as follows:

2 p.p. 100 million	Injury to certain vegetation
1 p.p. 5 million	Inhibition of enzyme activity
1 p.p.m. (water)	Reduction in dental caries
2 p.p.m. (water)	Mottled enamel (first 8 years of life only)
5 mg. per litre (urine)	No osteosclerosis
8 p.p.m. (water)	10% incidence of osteosclerosis
20–80 mg. per day (ingested)	Crippling fluorosis in 10–20 years
50+ p.p.m. (water)	Thyroid changes
100 p.p.m. (water)	Retardation of growth
125+ p.p.m. (water)	Kidney changes
2·5–5 g. (ingested)	Lethal single dose

Metabolism

Extensive studies of the metabolism of fluorides in the human body have been made in the Kettering Laboratory of the University of Cincinnati. The output of fluoride in the urine and fæces of volunteers who were given up to 12 mg. per day of fluoride was determined at regular intervals over a period of 130 weeks.[20–23]

96–97% of ingested fluoride is absorbed in the alimentary tract. Of the simple fluorides given experimentally, roughly half the dose was excreted in the urine, and half retained, mainly in the skeleton. Only unabsorbed fluorine is excreted through the alimentary tract. Some of the complex fluorides, such a sodium fluoroborate, are readily absorbed but are completely excreted unchanged in the urine. Normal persons soon attain a balance between intake and output—probably after a rough equilibrium is established in which the tissues, primarily those of the skeleton, reach and maintain a certain level of concentration. With an abnormally high intake, more fluoride is retained until the body reaches " saturation ", when the rate of accumulation decreases. This retained fluoride is gradually and slowly released at a progressively diminishing rate, once the intake of fluoride is reduced. Some is undoubtedly retained more or less indefinitely, but the process of skeletal retention is in a practical sense reversible.[24]

The concentration in animal bone associated with fluoride intoxication exceeds 5000 p.p.m., 3000–5000 p.p.m. occupying the marginal zone. Saturation point in cattle is 15,000–20,000 p.p.m. (" normal " 500 p.p.m.), and this is also approximately true for the human body.[25]

Fluoride is excreted in the sweat, particularly in hot weather, in concentrations which vary directly with the intake and the absorption.[26] The possibility that it may also be excreted into the stomach as hydrogen fluoride seems unlikely, although it has been suggested by some workers as an explanation of the gastric symptoms of fluoride intoxication.

Studies of the intake and output of fluorides show that a balance is achieved up to an intake of 8 mg. per day: at higher levels, about a fifth to a sixth of the intake is retained.[24]

For a normal intake, the urinary excretion of fluoride in man is about 0·5–1 p.p.m. (at a specific gravity of 1·02). For cattle and sheep, the urinary fluoride is 1·0–6·0 p.p.m. (at a specific gravity of 1·03). In cattle, a urinary output of about 10 p.p.m. or more indicates either increased ingestion of fluoride or the elimination of skeletal stores; it is usual to find values of 20–50 p.p.m. in cattle grazing on moderately contaminated pastures.[13] The excretion in the urine reaches its upper limits at 70–80 p.p.m. and cannot easily be increased beyond this.[25] Osteosclerosis is not as a rule found in the United States when the urinary excretion is less than 5 mg. per litre. In Southern India, however, 32% of those who drink water containing 2·5–5·0 p.p.m. of fluoride develop osteosclerosis, although the concentration in the urine may remain below 5 mg. per litre.[19]

The ingestion of water containing up to 4 p.p.m. of fluoride does not result in any accumulation in the heart, lungs, kidneys, liver, or spleen, and these tissue levels do not vary with an increasing concentration of fluoride in the drinking water. The aorta contains more fluoride than any other soft tissue, but there is no correlation with water-borne fluoride. The amount of fluoride in the aorta correlates well with age, and is probably associated with increasing calcification.[27 28]

In a series of necropsies in Utah County, Utah, made between 1955 and 1957, the highest fluoride-level in the tissues (both soft and osseous) was found in association with long-standing pyelonephritis. This agrees with the findings of earlier workers that renal disease may impair the excretion of fluorides, although it would be unwise to infer that there was a causal relationship between fluorides and renal disorders.[29]

Analyses of human renal calculi have shown that the amounts of calcium, phosphorus, and fluorine in the calculi were unrelated to the fluoride content of the drinking water.[18]

The fate of air-borne fluoride is of importance because of its relation to industrial hazards. When hydrogen fluoride or fluoride dusts are inhaled, most of the excretion takes place in the urine, although the fæcal elimination is greater than if the fluorides were ingested. An unexpectedly large and rapid increase in the urinary fluoride occurs, which is approximately the same whether gaseous hydrogen fluoride or a fluoride-containing dust is inhaled. No explanation has been found for this phenomenon.[29]

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In an experimental study, none of the volunteers who inhaled hydrogen fluoride complained of more than a slight redness and desquamation of the skin, and then only at exposures of 3·39 p.p.m.[24] On the other hand, several of the patients included in Waldbott's series [30 31] of cases of fluoride intoxication complained of itching and dermatitis after drinking water fluoridated at 1 p.p.m., or even after washing in it.

Fluorosis

"Fluorisme" was first described in France in 1930 as an occupational disease.[32] Soon after this, Møller and Gudjohnsson [33] found the same disease among Swedish miners during routine examinations for silicosis. Møller is credited with being the first worker to notice the characteristic radiographic changes of chronic fluorosis. 5 years later, Roholm [34 35] published his classic researches on the subject.

Most of the original cases occurred in those engaged in the recovery of aluminium from cryolite—a double fluoride of sodium and aluminium, containing some 54% of fluorine—but it is now known that there are about 28 industrial occupations and trades associated with fluoride hazard, including brickmaking and the calcining of ironstone.[13] Some of these, as well as affecting man, may also lead to fluorosis in cattle.

Signs and Symptoms

No one sign is pathognomonic of chronic fluorosis in either man or animals: the mottling of dental enamel is usually regarded as a sensitive diagnostic criterion, but it can only appear when the fluoride has been ingested during the formative period of the teeth. Mild dental fluorosis is found in cattle grazing near collieries and power-stations using low-grade coal, and may be the only sign of an abnormal intake.[13]

Mottling is often seen in the teeth of children who have lived all their lives in areas where the fluoride in the drinking water never exceeds 0·1 p.p.m., and may be an indication of fluoride deficiency. Observers not specially trained might be deceived by the enamel dysplasias produced by systemic disorders (cœliac disease can produce a condition closely simulating advanced dental fluorosis, and a severe attack of one of the exanthematous fevers can cause bizarre, often pigmented, enamel malformations).

The early changes of fluorosis can be detected only radiographically, and include increased opacity of the bones and calcification of the ligamentous attachments. The first changes are usually seen in the pelvis and in the lumbar region of the spine. Calcification of the sacrospinous and sacrotuberous ligaments is said to be reliable evidence of early fluoride osteosclerosis.[36]

In cattle, the first sign is often lameness, which is unaccompanied by arthritis, although the vascularity of the bone and periosteum is increased. The lameness is usually due to pathological fracture of the os pedis, and healing takes place rapidly if the animal is kept away from fluoride-contaminated foodstuffs. In severe fluorosis, the bones become fragile and porous, and, although bulky, are actually of lower density than normal.[16]

Human beings living in high-fluoride areas do not seem any more liable to fractures, and, when they do have fractures, healing is not delayed. Crippling osteosclerosis does not usually arise for at least ten years after the first ingestion of fluoride. Several cases of extreme osseous changes with ankylosis of the vertebræ were reported a few years ago from a moderately high-fluoride (about 7 p.p.m.) area in China. In one case, death followed fracture of the spinal column after a slight fall.[37]

Survey Findings

In a ten-year investigation of 118 persons, who had used a water-supply containing fluoride at 8 p.p.m. for over thirty years, no significant adverse effects, apart from dental fluorosis, could be found. There was no unusual incidence of skeletal fractures, arthritis, hypertrophic changes in the skeleton, or delay in the healing of fractures. In 10–15% of the 118, there were slight and ill-defined changes in bone density.[18]

A radiographic survey was made of 546 people between the ages of 30 and 70 in Framingham, Mass., where the water is naturally fluoridated at less than 0·1 p.p.m. No less than 229 cases of osteoporosis were discovered, of which 77 were severe and advanced. Various other bone abnormalities were found in greater numbers than in the Bartlett area (fluoride 8 p.p.m.). This lends support to the hypothesis that there is an optimum level of fluoride for proper bone development.[18]

A further study of 170,000 patients, mainly from Texas and Oklahoma, whose drinking water had never contained less than 0·7 p.p.m. of fluoride, gave broadly similar results. Fluoride osteosclerosis was detected in only 23 cases, all of whom had used water with a fluoride content of 4–8 p.p.m. for long periods.[36]

In India and the Far East, fluoride osteosclerosis seems to be commoner than elsewhere. Siddiqui [38] reported 32 cases of severe fluoride intoxication from water with fluoride concentrations between 5 and 12 p.p.m. 14 of these cases were associated with a fluoride content of 6·8 p.p.m. or less. The ages of the patients ranged from 22 to 50 years of age, and the symptoms appeared any time between the 25th and 40th year. Rao [39] described a case of paraplegia from fluorosis in a 45-year-old man. The water-supply contained fluorine at 7·2 p.p.m., but the urinary fluoride of the patient was never greater than 3·3 p.p.m. The paraplegia was caused by compression of the spinal cord from changes in the vertebræ.

A case in which the part played by fluoride is more doubtful was reported from the United States some years ago.[40 41] The patient was born in Texas in a region where the water contained 1·2 p.p.m. of fluoride. (In the original account, the fluoride content was given erroneously as 12 p.p.m.) He lived there for the first seven years of his life, then spent two years in an area where the water contained 5·7 p.p.m. of fluoride, and finally moved to Lubbock, Texas, where the water contained 4·4 p.p.m. of fluoride. He died at the age of 21, and, at necropsy, fluoride osteosclerosis, anæmia, kidney damage, and other degenerative abnormalities were found. The only obvious symptoms during life were mottled teeth (also possessed by his sister), and complaints of tiring easily. Other similar, but less severe, cases have been reported from Lubbock and from Dallas.

Waldbott's cases [30 31] are more peculiar because they all occurred in areas where the fluoride content of the drinking water was 1·0 p.p.m. or less, and because of the variety of symptoms complained of by his patients. These symptoms included stomatitis, dermatitis, gastric pain, dysmenorrhœa, and parasthæsiæ and weakness in the limbs—often all in the same patient. The neurological symptoms could, perhaps, be explained by the anti-oxidase activities of fluoride, but the dramatic suddenness with which all symptoms disappeared when the patients were given fluoride-free water is hard to account for. No mention is made of whether any of these patients were tea-drinkers.

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Unsolved Problems

The relation between intake and permanent deposition is not known, nor is the influence (if any) of tea-drinking and fish-eating. Certainly fish-eating has not checked the increase in dental decay among the inhabitants of Tristan da Cunha, where the dental state has gone from excellent to poor in a mere twenty years.[42] There is probably some dietary factor concerned here, since the Tristan da Cunhans now receive regular supplies of "civilised" food, and more knowledge is required of the general and local effect of fluorides in conjunction with different types of diet.

The mechanism which induces fluoride osteosclerosis is unknown: it is likely to be a modification of some enzyme reaction, but which enzyme is concerned is a matter of conjecture. Nor is it known why the lumbar region of the spine is preferentially affected, or why fluorides should alter the functioning of the ameloblasts. Arthritic bone contains normal concentrations of fluoride[19] and yet there is a greater tendency for hypertrophic changes in the vertebræ of those who live in low-fluoride areas. Much available evidence suggests that there is an optimal absorption, but one which has yet to be determined with certainty.

Removal of Fluoride and the Alleviation of Fluorosis

No compounds are known that will completely prevent the toxic effects of ingested fluoride, but compounds of calcium and phosphorus have been found to reduce the toxicity in small laboratory animals, and there is some evidence that a similar effect can occur in cattle and sheep. 0·5% of aluminium sulphate added to rations containing up to 50 p.p.m. of fluoride reduces the absorption of fluoride by cattle by about 30%.[45]

Ion-exchange resins have proved efficacious under laboratory conditions.[12] 1 μg. of fluorine can be recovered with a reproducibility of ± 0·5 μg., and the recovery of fluoride may be greater than 95% of that known to be present. Conceivably a cheap ion-exchange defluoridator could be produced for use in the home by those who wish to avoid any increase in their fluoride intake.

Industrially, water fluoridated at 1 p.p.m. presents no difficulties—in fact, it is welcomed by brewers who find that it helps to control the numbers of "wild" yeasts that are often present.

Fluorosis and Industrial Waste

More than 4400 tons of fluorine are discharged annually into the atmosphere of the British Isles during the manufacture of superphosphate fertilisers.[44] The social consequences of this and of other processes liberating fluorine have been discussed by Murray and Wilson.[45] They point out that fluorine intoxication occurs not only as an industrial disease, but also as a "neighbourhood" fluorosis, near such places as aluminium factories and brickworks. Some of the earliest cases were reported from Bedfordshire, where marine clay is used for brick-making.[46] Agricultural workers complained of respiratory distress, and farm animals showed signs of advanced osteodystrophy. Murray and Wilson described an outbreak of fluorosis affecting a farmer and his family, who lived in an area of Lincolnshire where ironstone calcining was carried out.[45]

Murray and Wilson consider that the hazards of gaseous industrial wastes containing fluorides are not sufficiently appreciated in this country, and that the extraction of fluorine from fumes should be practised more extensively. They suggest that records should be kept of the location of all processes creating a potential fluorine hazard.

* * *

The position is summed up by Kehoe[47] who says: "... it is inevitable that fluoride is incorporated in the chemical composition of living organisms, including the human organism. Even if it were not involved usefully in certain processes of the living organism, the certainty of its presence within the organism establishes the fact that fluoride is ... part of the internal environment of the human organism. It cannot, in this relationship, be, in itself, harmful. In appropriate concentrations it enters into specific reactions which are beneficial".

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Congresses

MENTAL HEALTH

THE 13th annual meeting of the World Federation for Mental Health was held in Edinburgh from Aug. 8 to 13, under the presidency of Dr. PAUL SIVADON, chief medical officer, psychiatric hospitals of the Department of the Seine, and professor of psychiatry, Brussels. Approximately 750 people from 43 countries attended. The theme of the meeting was Action for Mental Health.

In a presidential address on the Need for Science and Action for Mental Health, Professor SIVADON spoke of the opportunities which are now arising in the under-developed countries, as well as in the more developed areas, for both public and private action to improve the mental health of people, and he emphasised the need for mental health to develop its own specific interdisciplinary and intercultural scientific bases of action.

The first plenary session was devoted to a demonstration discussion group on the techniques of communication, in which representatives of six countries took part. Dr. LAURETTA BENDER (New York) outlined a scheme for providing for the care of emotionally disturbed adolescents; and Dr. DONALD BUCKLE, regional mental health officer for W.H.O. in Europe, spoke on the community services for subnormal children with an emphasis on prevention and early recognition, drawing attention to the resurgence of interest in the ætiology and prevention of mental defect.

Professor SARKISOV (Moscow) spoke on the theory of brain structure and function, and gave a brief account of some of the more significant advances in neurophysiology. Prof. H. C. RÜMKE (Utrecht) followed with a paper on the identification of mental disorder and its causes, and declared that two aspects must be distinguished: (1) how to identify a patient as mentally diseased, and (2) having done this, to discover the nature of the disorder and its causes.

The fifth plenary session was devoted to action in the refugee camps. Dr. HANS STROTZKA, mental health adviser to the U.N. High Commissioner for Refugees, outlined the social and psychiatric measures now being adopted for the residual long-term refugee groups. It is now becoming evident that the psychiatric disorders of long-term refugees, though striking in their clinical forms, are not as numerous as anticipated and, on the whole, have a better prognosis than disorders of purely psychogenic origin that have a similar clinical picture.

Dr. ALEXANDER REID MARTIN (New York) spoke on mental health and the rediscovery of leisure, and suggested that

society's efforts at present to free more time from work activities must be regarded as a great experiment. Prof. T. FERGUSON RODGER (Glasgow) spoke on the mental health training of professional groups. He attached great importance to the reintroduction of the clergy to the role of counsellor in psychological problems. Mental health action in industry was reviewed by Dr. M. R. VAN ALPHEN DE VEER (Eindhoven), who spoke of the conflict between technological development and that of the individual, and emphasised the need for good communication.

In a session on mental health and growing old, Dr. NAIRN R. COWAN (Rutherglen, Lanarkshire) described the work of the Consultative Health Centre for Older People, Rutherglen. In a series of 1000 men and women, emotional stress was observed in about a quarter. The commonest causes of stress appear to have been adverse home environment and bereavement.

The Dr. Mary Hemingway Rees memorial lecture was delivered by Prof. HENRI BARUK (Paris), who spoke on Hebrew Civilisation and the Science of Man.

At the annual general session of the Federation, Prof. Pacheco e Silva (Brazil) was inducted as president for 1960–61. Dr. George S. Stevenson (U.S.A.) was elected vice-president (president 1961–62). Sir Geoffrey Vickers was elected treasurer. The following were appointed to the executive board: Dr. T. Baasher (Sudan), Dr. W. A. Dibden (Australia), Prof. O. Klineberg (U.S.A.), and Dr. Hans Strotzka (Austria). Dr. J. R. REES, the director, addressed the general session on the topic Are We Making Progress? The opportunities of the Federation and its members in all corners of the world are immense at the present time, but the work of the Federation continues to be hampered by lack of adequate regular financial support. World Mental Health Year, despite lack of adequate finance for central projects, created great interest and gave rise to a very encouraging volume of new work.

INDUSTRIAL MEDICINE

THE 13th International Congress on Occupational Health, which met on July 23–29 in New York, was attended by about 1200 doctors, nurses, and allied workers representing 44 countries. The congress, which is held every three years, was organised by an American committee on behalf of the permanent committee and the International Association on Occupational Health. Dr. LEO WADE was president of the congress and chairman of the organising committee.

In the inaugural address Prof. SVEN FORSMANN (Sweden) referred to some of the problems of occupational health still to be solved—for example, those introduced by increasing mechanisation and automation of industry and by the rapid industrialisation in developing countries. Mr. MARION D. FOLSOM, a former United States Secretary of Health, Education and Welfare, in the keynote address, spoke of the " exciting new challenge to occupational health ", but he emphasised the many unsolved difficulties of the past, among them the hazards of exposure to chemicals and radiation. He made a plea for international cooperation as one of " the most promising means for the solution of occupational health problems " and advocated the establishment of properly coordinated international centres to exchange information, undertake research, and act as training centres.

We publish below brief notes of some of the other contributions.

Prof. G. C. E. BURGER (Netherlands) described the industrial physician's experience of human behaviour in industry and held that his insight into human reactions in physiological and pathological conditions made him a worthy adviser on job analysis, work organisation, and work design.

Discussing the design of information Dr. R. CONRAD (England) showed that only 20% of a group of subjects of average intelligence were able to follow correctly official instructions in order to get an incoming telephone call transferred to another extension.

Prof. E. C. VIGLIANI (Italy), opening the session on education and training, pointed out that in each country the development of occupational medicine had been different: thus, in Germany it was derived from pharmacology, toxicology, and hygiene, while in France its source was legal medicine, in Italy internal medicine, and in Spain traumatology. Teaching varied considerably in different countries: in some, occupational medicine was an independent subject and in others it was part of different disciplines. Training of industrial physicians in the Western hemisphere was described by Dr. F. PRINCI and Dr. R. A. KEHOE (U.S.A.), and Dr. L. SILVERMAN (U.S.A.) dealt with the training of industrial hygienists in the West. Dr. A. A. LETAVET (U.S.S.R.) gave an account of the training of industrial medical personnel in Russia.

Dr. P. H. ROSSIER (Switzerland) said that pneumoconiosis was often complicated by chronic bronchitis: among his patients 49% of those between the ages of 25 and 40 showed evidence of bronchitis and over the age of 41 the figure increased to 57%. Dr. G. CADARIU and his colleagues (Hungary) illustrated the incidence of silicosis in the foundry industry: out of 1330 workers, 55 (4·3%) were borderline cases described as presilicotic forms, and 54 (4·0%) were cases of silicosis of the 1st and 2nd degree. No 3rd degree cases or cases of silico-tuberculosis were found. Dr. E. O. COATES, Jr., and his coworkers (U.S.A.) described the relationship of chronic bronchitis to dust exposure in an industrial community. Chronic bronchitis was defined as the presence of a cough lasting at least six months and productive of more than 1 teaspoon of sputum per day. 1341 men aged 40–65 working full-time in an industrial community were surveyed by means of a questionary, chest film, and spirographic studies. They were divided into four groups: those without industrial exposure, those with industrial exposure but without a silica risk, and those exposed to a silica risk in a foundry (*a*) without X-ray evidence of silicosis and (*b*) with X-ray evidence of silicosis. Results disclosed a surprisingly high incidence of bronchitis in all four groups.

Professor VIGLIANI (Italy) and his coworkers described the acute toxic effect of particulate silica and described experiments in which intravenous injection of 10 mg. of fluoric-acid-etched quartz tridymite cause the death of 50% of albino mice in two to eight days with hepatic and splenic changes. The death of the animals was attributed to failure of the reticulo-endothelial system to detoxify endotoxins absorbed from the intestinal tract.

Dr. J. MCG. ROGAN, Dr. J. FAY, and Dr. S. RAE (England), in a preliminary report on the work of the National Coal Board Pneumoconiosis Field Research, said that 35,000 coalminers were regularly X-rayed, given pulmonary function tests, and asked to complete a questionary. An analysis of the data on 10,000 miners was presented.

Dr. G. DINISCHIOTU (Rumania) and his coworkers described the results of long-term corticotherapy on rapidly developing silicosis. They believed that corticosteroids had excellent general effects and may even stop the development of silicosis.

Dr. KATHERINE WILLIAMS (England) discussed the application of radiation and radioactive materials, and reviewed progress and future trends. There was considerable evidence that prescribed radiation levels were sufficiently low to prevent detectable somatic damage, but it was now realised that doses of radiation of no known significance to the individual may have genetic consequences. All concerned with radiation protection must contribute to the education of the worker and help both present and future generations to learn to use radiation as safely as electricity and mechanical devices in industry. Dr. N. WALD and Dr. G. THOMA (U.S.A.) dealt with radiation

accidents in nuclear technology. Industrial radiation accidents were divided into major and minor categories, and the major group included 7 accidents, 5 in the United States. Results ranged from no clinical effects in 14 cases to death in 3 cases.

Miss D. M. WARNOCK (England) illustrated the work of an industrial nurse in a hospital occupational health unit; Miss M. D. SCHMIDT (U.S.A.) spoke of the task of the nurse-supervisor in a nursing service of multiple units; and Miss G. BISSONNETTE (U.S.A.) discussed the role of the nurse-consultant.

A panel discussion on the American concept and experience of small plant health services in Canada, Central and South America, and the United States was presided over by Dr. L. MCGEE (U.S.A.); and the European outlook and experience was given by a panel whose moderator was Dr. R. S. F. SCHILLING (England). Although the establishment of an occupational health service to cover all employees at their place of work was advocated by some speakers, the subsequent discussion made it clear that this view was by no means universal.

Dr. G. F. KEATINGE and Mr. A. BOX (England) gave a comparative study of two matched groups of accident, sickness, and absence records. They concluded that the differences observed in accident figures reflected at least in part different propensities on the part of individuals to report minor injuries. Dr. LAWRENCE E. HINCKLE, Jr., and his colleagues (U.S.A.) had studied the continuity of patterns of illness and the prediction of future health, and they believed that past patterns of disability predicted future patterns with modest accuracy.

Dr. A. L. POTTER (England) referred to the need for international cooperation in toxicological research, and he made a plea for the establishment of some international body in a position to assess the value and reliability of clinical tests, questionaries, and scientific experiments, which could issue authoritative statements for use throughout the world.

Dr. E. KING and Dr. A. THOMPSON (England) described a field survey to determine the relative significance of tests for lead absorption and poisoning, and they concluded that the value of any one test or combination of tests depended on the laboratory facilities available and the experience of the person interpreting the results. In many small factories simple qualitative coproporphyrin estimations could give a measure of protection at present lacking. Dr. S. G. RAINSFORD (England), describing laboratory aids in the supervision of lead workers, also emphasised that coproporphyrins could be estimated quantitatively by simple means without the need for expensive equipment.

Dr. F. C. DOHAN and his colleagues (U.S.A.) described the surgeon's opinion as a major factor in the prolongation of uncomplicated surgical convalescence. They suggested that the majority of patients were advised to undergo far longer convalescence after the common surgical operations than was necessary and that this resulted in unnecessary iatrogenic illness as well as economic loss to the individual and to society.

Dr. R. E. W. FISHER (England), discussing the relationship between molluscum fibrosum and tar wart, held that there were two types of tar wart, one of which was indistinguishable from molluscum sebaceum, and that this lesion was rarely seen on hairless skin and nearly always regressed spontaneously, except on the scrotum.

Dr. E. C. STEELE (Canada) described the Ontario rehabilitation programme for occupational injuries, which has been sponsored by the Workmen's Compensation Board, the body responsible for the rehabilitation of the injured workman. The approach was novel and interesting, and its success seemed to have been achieved largely by the good personal relations between patients' doctors and the rehabilitation consultant, who was also at the disposal of the workman.

Professor FORSSMAN took the chair at the closing plenary session, when Dr. WADE re-emphasised the worldwide nature of the problems of occupational health and the need for free exchange of information and for cooperation, which could be potent instruments for peace.

Occasional Book

THE PHENOMENON OF MAN

LIKE question and coin Pierre Teilhard de Chardin's book [1] has two sharp sides. Its great announcement, high authority, and its noble reconciliation of religious and scientific thought, these are the features which will have put the book in the reader's hands in the first place, and as he puts it down he is not resentful. Against this, the language, which is that of a scientist, the neologisms, its Roman snow cap, the feeling that most of it has been said before, this celestial banality, these lead to doubt: perhaps the book is noble, and no more.

Admittedly blue-sky literature is now so common that it must read commonplace, and it is not perhaps fair to be bored with the problems because the solutions sound unsatisfactory, but so much of Father Teilhard's ground is trodden. Take the " within-without " argument, for example: Europe has had this for years; Kant just about showed that it could not be solved in words while Cézanne had the luck to produce a solution in paint but how he did it is still inexplicable; between them they have left priests and scientists nowhere in the chase. Then there is this feeling of inevitability of the thing: this is not a book about evolution but a prophecy of how evolution must work out over the next ten million years. Again the German philosphers smelt the same rat and this section is very redolent of Hegel's theory of history. There is the same fatality too about Father Teilhard's comparison of minuscular biology with the momentous. " Groping ", "infolding ", these are the sort of terms we get; biology is the same according to this parson whatever the size or the stage of the living thing observed: one wonders if it is. Certainly Man can now defeat Nature any day he likes and the present problem is not his delivery or adjustment to prison but how he can remain Promethean without his chains.

The book is haunted with " universality " and " comparative this and that " but most scientists have this trait these days; they exclude everything else. Thus, there is only one space to Father Teilhard, universal space: he says that. But space is not even physical, always; the æsthetic space of art is just as real, and even within this narrow field space is vastly different for sculpture and for painting. It seems a strangely illiberal attitude to wipe space off, as astronomic and atomic only. In the same way Father Teilhard pronounces on "omega" and "megasynthesis": he is convinced of " convergence " and obsessed with " synthesis ", so that biology becomes a scatter and a secondary collection, a cycle between " radial " and " tangential " energy. But how can he be so certain? Man's mind might fly off tangentially in any direction and it does not have to be controlled by the modern " scientific enlightenment ", which may prove to be no more accurate than any other enlightenment, and even if it stays accurate that is not to say that man will always bother with it. The great scientists of today are just as likely to end

1. The Phenomenon of Man. By PIERRE TEILHARD DE CHARDIN. Translated by B. WALL. London: Collins. 1959. Pp. 310. 25s.

with the same reputation as the Rosicrucians of three hundred years ago.

While the early part of the book is little more than Wellsian the last section, on Survival, is more frightening. He begins by saying that isolation is to be avoided, but he seems to confuse individual isolation (existentialism) with group isolation (racialism); and true to his obsession and keeping his eyes on "omega" he goes on to say that the Universal and the Personal grow in the same direction and culminate "simultaneously" in each other; personality moreover is a prison from which we must try and escape. Now if he had said scientific theory is a prison from which we must try and escape . . . however, a chapter is reached, Love as Energy, and hope is regained; this Frenchman then is like all other Frenchmen, a Beylist at heart. True, Stendhal would have preferred to say that love is energy, but this title sounds near enough, but alas, that is as near as the title does get. Father Teilhard's love, like everything else he describes, is both molecular and universal; it is a union, but one subject to the force of physico-chemistry, not to happy chance, nor to any aim of ideal; it certainly has no relation to the grand European conception of love, as a *moment* when the conscious and unconscious suddenly meet in cross pelt and grip, a welding point of voluntary and involuntary. What Father Teilhard describes is much colder; it is the intellectual awareness only, without the sensation of glory, and he calls it the rise of consciousness, of which the recognition of evolution itself provides to him the obvious example. This collective consciousness is a verbal corollary of the collective subconscious, either being necessary for the other, and so the *carrousel* of language circles the electronic organ. The book's word forms are its most hideous feature and the translator deserves every sympathy, and praise, because his result is easily readable and intelligible.

We know by now that there are far bigger cosmic powers than ourselves. Man indeed has long suspected it but relativity and evolution have made it certain. Father Teilhard finds this depressing and a source of modern unquiet, but should the certainty really be very different from the previous suspicion? Man's real hope remains as before, in himself, and his power of suprahumanity is his salvation: this is the God on Earth we recognise as Christ, an available divinity in human shape. Father Teilhard does not seem to grant a tittle of this divinity to man, and the Catholic authorities probably excluded his work from their shelves on this score alone. Being antagonistic to human spirit the book might also be criticised on lesser humanistic grounds. Man will surely regret it if he allows himself to be poured into this bottle of "forced coalescence", to take another of Father Teilhard's terms.

Public Health

Poisoning from Organophosphorus Compounds used in Agriculture and Horticulture

WE are grateful to the Department of Health for Scotland for the following information to supplement that in our issue of July 23 (p. 201).

The following arrangements have been made to cover Scotland:

Supplier of P2S.—Law Hospital, Carluke, Lanarkshire. Telephone: Wishaw 621.

Blood-cholinesterase estimation.—The following laboratories can carry out estimations of cholinesterase activity of blood samples: Biochemistry Laboratory, Edinburgh Royal Infirmary; Biochemistry Laboratory, Glasgow Royal Infirmary; Biochemistry Laboratory, Maryfield Hospital, Dundee; Biochemistry Laboratory, Aberdeen Royal Infirmary.

In England Now

A Running Commentary by Peripatetic Correspondents

CAN any other people match the Swiss when it comes to replacing a bridge in a hurry? The other day we joined a queue of halted cars in a storm beside Lake Brienz. I despatched my youngest amid lightning, thunder, and drowning rain (which, as we pushed him out, he sourly termed "the lot") to discover the cause. A ten-foot bridge traversing a small ravine had just been destroyed by the torrent beneath: half its breadth had disappeared, while the other half drooped indeterminately without support. What to do? Many cars turned back; but the map told us that our only alternative route would take us half round the country, so we decided to wait. We were right. Almost within the hour the bridge was reopened to single-line traffic.[1] In that time a gang of twelve men arrived, with pikes heaved massive trunks longitudinally into concrete slots, and laid planks transversely. As we made our grateful way over the restored bridge towards Interlaken, the first policeman arrived on a motor-bicycle. In England, now, the policeman would have turned up promptly; but what about the gang of twelve? We like the Swiss way. C'est pratique.

* * *

My friend Giles was accident-prone for a fortnight; and that, he swears, was long enough. Soon after we arrived on holiday he chanced to see a tall blonde goddess watching his tennis. This inspired him to such Hoad-like activity that he won his match. Alive to the fullness of the moment, he rushed across the court and leapt the net. Unfortunately, he did not quite make it. He met the young lady a few evenings later at the weekly dance. She was a nurse, he discovered, when she gave him first-aid for the cup of tea he cascaded into his left shoe. Probably on the principle of humouring the patient, she agreed to go sailing with him the next afternoon.

At the appointed time Giles escorted her aboard the waiting dinghy. Despite some spirited poling with an inverted oar the boat refused to budge from its bed of sand. Nothing daunted, Giles slid over the stern and gave a few manly pushes under the expectant gaze of his lady. Still the vessel remained fast until, at last, with a superhuman heave he set it in motion. Unhappily, at the same time, he stood on a piece of seaweed. As the dinghy surged forward Giles dived headlong into the deep blue sea. The rescue operation was interesting: Giles, dazed and dripping, was hauled to the shore while a boat was launched in pursuit of his companion, who, being no sailor, was gliding helplessly out over the bay.

How he managed to persuade her to walk with him the following evening is beyond my comprehension; but, as the sun set, they were strolling along a country lane, Giles relating how he had won a medal for the high jump at school. Should she care, he would demonstrate the style that had won him this honour. The look of awful anticipation on her face did not escape him, but, he said, not to worry, he would do no more than demonstrate on that three-foot wall. The plaintive wail and dull thud which followed his disappearance, if not new, was still alarming. Rushing to the wall and looking over she beheld Giles on his back, groaning, in a sunken field six feet below road level.

Giles has had fewer accidents lately. His wife, a tall blonde girl, takes good care of him: she says he evokes her nursing instincts more than any patient ever did.

* * *

A week or two ago in the *Guardian* Mr. Michael Frayn, prompted by the Knossos controversy, gave us the outline of an archæological discovery 2000 years hence of relics relating to a man called On Her Majesty's Service ("On" to his friends) who died in the nuclear cataclysm which ended what Mr. Frayn calls the Neoplastic Age. The moral of the story was that the interpretation of ancient scripts (particularly those that can't be found) is not a very exact science.

The learned references in these columns [1 2] to William of

1. *Lancet*, 1960, i, 1246.
2. *ibid.* Aug. 6, 1960, p. 302.

Occam and his Razor lent further point to the moral and left at least one reader more than ever uncertain what the Sage really said or meant. But I also have a personal interest in his remarks.

Our family coat-of-arms, as it happens, is composed of three rather tatty hedgehogs, with the motto *Frustra per Plura*. It is clear that whoever devised these arms used *his* Razor to adopt Occam's dictum [3] to his own ends. Nothing wrong in this, of course—just good clean heraldry. And at first sight, at any rate, the motto looks grand. It tells us that the hedgehog baffles its enemies by the multitude of its points, and clearly implies that my forefather was an unusually versatile man. (I try to suppress the thought that the hedgehog is also reputed to accommodate more fleas to the square inch than any other animal.)

But what worries me is the premonition that one day some fresh authority will come along and assure us firmly that William of Occam was not redistilling the wisdom of Aristotle [3] at all, but quoting from the (unfortunately untraceable) writings of an obscure Roman philosopher, Empiricus Maximus, and that what he said was simply *Frustra per plura*, meaning " The more hypotheses the better—they can't *all* be wrong ", or, more simply, " Just keep on guessing, brother, and one day you'll guess *right*."

PS.—Last night I dreamt I saw William of Occam trying to shave a hedgehog.

* * *

We have grown accustomed to cocktail cabinets disguised as bureaus, television sets disguised as cabinets, and radiograms disguised as book-cases. I should not therefore have been surprised when a patient, unable to hear my interrogation in the dim red light of the X-ray screening-room, apologised as she adjusted her spectacles, saying that the noise of the X-ray machine upset reception on her hearing-aid. With a twist of part of the side-frames of the spectacles, she assured me that all was now well again. In better light I might have realised sooner that the spectacles had plain glass lenses, and I would then have adjusted my speech at the outset. She did not seem to have heard the old jingle:

> Safety pins and bassinets
> Are for the girl who fascinates:
> The girl who is bespectacled
> Never gets her neck tickled.

But it set me wondering whether there is not a fortune waiting for the man who can patent a pair of spectacles which is disguised as a hearing-aid.

* * *

Now I can imagine the author's thrill as he reads the public acclaim across the daily press headlines; the playwright's as he waits in the wings before he acknowledges the deafening applause with a stiff dignified bow; the composer's as, with champagne glass held aloft, he hears the music of his creation issuing pure and smooth from the record for the first time; the ballerina's as she curtsies before the footlights after the performance of her life; the architect's as he sees the child of his imagination rising splendidly above the skyline; the artist's as his picture is carried with reverence to its place in the Royal Academy.

All these things I know now. Not only has *The Lancet* published my paper, but after weeks of patient waiting the British Council have requested two reprints for a doctor somewhere in Yugoslavia.

* * *

On the conformity scale In America Now the eggheads come somewhere between the organisation men and status-seekers on one hand, and the beat and shook-up generations on the other. When they talk, as like everyone else they do, of the " space race " and the " missile gap " one of them is likely to murmur, " I hope our Germans are cleverer than their Germans." And they are telling the story of the international conference at which an English physicist complained that he could not understand one of the delegates. He was told that he should learn the scientific lingua-franca of today—Broken English.

3. Frustra fit per plura, quod potest fieri per pauciora.

Letters to the Editor

OUR POOR THAMES

SIR,—The Press and the medical profession have recently become aware of the pollution of our bathing beaches by untreated sewage. One of us, a riverside dweller, has noticed that the upper Thames (above Teddington Lock) often smells. Since bathing is encouraged in these waters, we felt constrained to examine some specimens of Thames water bacteriologically.

These specimens were collected at Staines on Wednesday, June 29, and Wednesday, July 13, at 6.45 A.M. The samples were taken 6 feet from the shore, 1 foot below the surface, into sterile 2-litre containers. Both specimens were received in the laboratory within $2^1/_2$ hours. There were no inhabited boats on the non-towpath side of the river for at least $^1/_2$ mile upstream, so the possibility of direct contamination was avoided. There had been a good deal of rain during the days preceding sampling, but river traffic midweek is light, since most hire cruisers are by then farther upstream.

The results are shown in the accompanying table. We think

SPECIMENS OF WATER FROM THAMES AT STAINES

—	Total colonies per ml.		Presumptive coliform count per 100 ml.	*Clostridium welchii* count per 100 ml.
	20°C after 72 hr.	37°C after 48 hr.		
Specimen 1 . .	280	433	900	not done
Specimen 2 . .	4000	2000	350	250
Drinking-water	No figures quoted		<50	0

the disturbing nature of these figures may best be understood by comparing our results with the worse acceptable figures for drinking-water given in the Ministry of Health report on *The Bacteriology of Water Supplies*.

This report states on p. 19: " It must be remembered that swimming bath water often inadvertently becomes drinking water, particularly where schoolchildren are concerned, and therefore the water in swimming baths should as nearly as possible reach the standard of drinking water ". It is apparent that, at the site of sampling, and presumably downstream, the river is extremely heavily contaminated. It follows that the river inevitably must at one time or another carry all the pathogenic bacteria and viruses that may be excreted in the fæces and urine.

We feel that this river may well constitute a major menace to public health, at least the last twelve miles before it becomes tidal, and below this point it is obviously unfit for bathing. Reluctantly we should like to suggest that bathing should be discouraged until such time as it takes to eliminate sources of contamination.

We hope this unpleasant spoiling of this beautiful river can be prevented. Perhaps enlightenment of the public and the display of bacteriological counts such as these with their sinister interpretation at bathing establishments might induce river users to refrain from further contamination of the river.

The Middlesex Hospital, London, W.1.

D. B. LONGMORE
R. E. M. THOMPSON.

SHORTAGE OF RADIOGRAPHERS

SIR,—The Society of Radiographers indeed welcomes any action which will draw the attention of the medical profession, or of any other interested body, to the present serious shortage of radiographers, and that offers the hope of a satisfactory solution of the problem, and the society's council has asked me to write to express its thanks to Dr. G. Osborne for his letter of July 9, and to you, Sir, for

having published it. But it has asked me to add the comment that it does not think the solution will be as easy as Dr. Osborne has made it seem.

The society has for many years, and in many directions, been seeking to improve recruitment to the profession. The secretary is constantly in contact with the Youth Employment Service, with schools, and with the representatives of many interested organisations. Careers exhibitions have been sponsored; in the past year some twenty thousand careers brochures printed and published by the society have been distributed throughout the British Isles; articles have appeared in women's magazines drawing attention to radiography as a career; and programmes with the same purpose have been featured in television and radio. Practically every member of my council has played a part in these undertakings. Most of them have attended schools and " careers conventions ", often in their own time and after exhausting days in their understaffed departments, often travelling at their own expense—but none of them have had the good fortune that appears to have attended Dr. Osborne's recruiting officer, not even those few who might approximate to her endowments in point of youth, warmth, and vitality. In fact, the results that Dr. Osborne reports are quite unlike those that we have had.

" We have suffered long enough from the shortage of radiographers," says Dr. Osborne. No-one has suffered more, or longer, than have we radiographers who have been left to shoulder the burden while our one-time colleagues have gone on to better-rewarded jobs, or to marriage. Our efforts to relieve the shortage have had the urgency that comes of the goad of necessity and circumstance. We think that our results must bear a closer relation to reality than can Dr. Osborne's single experiment.

We agree, Sir, with your annotation that it is vital that men should take up radiography. We agree with Dr. Osborne that radiographers' salaries are not large enough for men with family commitments.

We reconcile the two arguments by maintaining that salaries must be made large enough to attract men to the profession, and, what is more, to keep them in it.

E. R. HUTCHINSON
London, W.1. President, The Society of Radiographers.

DOUBTFUL PROGRESS IN PSYCHIATRY

SIR,—I think it would be unfortunate if the criticisms of recent trends in mental health by Dr. Oliver (July 30) were to go entirely unanswered. In the absence of more weighty intervention, perhaps I may offer a few observations.

The social catastrophes produced by psychosis are, as Dr. Oliver points out, well known to psychiatrists, but it may be expected that a much deeper awareness of these problems will result from the trend towards community services. The psychiatrist who is accustomed to domiciliary treatment and who has the benefit of information from social workers is more likely to appreciate what is happening to patients outside than one who is " institutionalised " in a mental hospital.

There seem to be two assumptions in Dr. Oliver's argument which may be disputed. The first is that we are leaving behind an era in which almost every seriously disturbed patient was committed to hospital. However, investigations such as those being conducted in Bethnal Green by the Institute of Community Studies indicate that degree of disturbance is not even the most important of many factors which have influenced admission to mental hospitals. Lack of social support may well have been the most influential of these factors, and it has still to be demonstrated that the socially isolated are finding it more difficult to secure admission. As community services extend, we may expect to become more aware of the problems which exist and to be more able to offer treatment and support (though not necessarily within hospital). Similarly, as Brown has pointed out,[1] discharge is a social process, in which the patient's clinical condition is only one of the factors involved.

The second assumption is that community services are a device to save money, by avoiding the improvement of mental hospitals. In fact, they are extremely expensive in terms of man-power and money.[2] To introduce community treatment as an economy measure would be most unwise; and there seems to be very little evidence that this was ever the intention. Substantial improvements continue to be made to mental hospitals even though, as Professor Hargreaves recently suggested,[3] some are " too remote, too vast, too inhuman and too primitive in their domestic and medical facilities to play a part in a modern mental health service, however much we were to spend on them ".

The necessity for some psychiatric cases to have prolonged inpatient treatment is scarcely disputed. Psychiatrists would not be helping the community, however, if they were to retreat to the mental hospitals, ignoring all the valuable developments of recent years which allow management in other settings. It seems likely that institutional treatment in the future may require buildings very different from most of our existing mental hospitals—for instance, something on the lines of the comprehensive hospital proposed by Professor McKeown. To concentrate all our resources on " improving " mental hospitals may merely remove the opportunity of future progress. The suitably placed mental hospital, however, can still play a valuable role as one partner in a community mental-health service.

Littlemore Hospital, Littlemore, Oxford. H. L. FREEMAN.

SIR,—How encouraging are Dr. Oliver's down-to-earth views (July 30) on certain modern trends in psychiatry. We hear talk of therapeutic communities, permissive atmospheres, group methods, and other clichés, and we become uncertain of their goal idea.

We should not, in our search for improvement, forget that conventional mental-hospital care has its good points. The need for its facilities cannot be removed by pretending that it has ceased to exist.

No doubt our mental hospitals will, with advances in treatment that will prevent the evolution of chronic psychosis, gradually become less crowded; but, unless I am mistaken, there is no overall trend which suggests that this is yet happening. With the biochemical advances already made and those which we hope are imminent, clinical psychiatry will soon, if indeed it has not already done so, take its place with clinical medicine.

The true basis for advance lies in time-honoured methods of clinical observation and study in conjunction with laboratory technique and research; and the mental hospital as it stands is not an inappropriate place for this to be done. Some directions of current thought are away from this, and their aims and rationale are obscure. The excessive open-door policy has done nothing constructive in itself. The policy, desirable up to a point, has, in fact, been made possible only through the agency of modern physical methods of treatment. Without other facilities in sufficient abundance for patients to be supervised and given something purposeful to do it is a mixed blessing.

The greatest single outcome of the increased public concern and interest in mental health and illness will, one hopes, be an increased recruitment to nursing. This will enable our work to achieve its fullest scope in a way that no amount of legislation, planning, or revolution will do.

Carlton Hayes Hospital, Narborough, Leicester. JOHN CLEOBURY.

1. Brown, G. W. *Acta psychiat.* 1959, A 96.
2. Colwell, C., Post, F. *Brit. med. J.* 1959, ii, 214.
3. Hargreaves, G. R. *Daily Telegraph*, July 11, 1960.

DISPOSABLE UNDERPADS FOR INCONTINENT PATIENTS NURSED AT HOME

SIR,—Dr. Roberts and Miss Mann (July 23) discuss disposable underpads for incontinent patients nursed at home, and suggest the use of those obtained from Johnson & Johnson. May I describe my own experience with them? My invalided mother was the patient.

First there is no adequate material to take care of fæcal incontinence, provided the stool is not diarrhœic. Fæces cling to anus, buttocks, and pad. As for urinary incontinence, Johnson & Johnson underpads will take care of dribbling, but cannot sop up the massive gush. The result is an overflow of urine on to the bed sheets.

Trial and error produced what proved to be a satisfactory device. Several layers of 'Cellucotton', totalling about 3 in. in thickness, are enclosed in a continuous sheet of paper towelling. The latter holds the absorbent material together when wet by urine. The pad, thus enclosed, rests on many thicknesses of newspaper beneath which is a plastic sheet of somewhat larger dimensions to keep the bed sheet dry.

When the wet pad is to be removed, the patient is turned as when changing the bed linen. The plastic sheet is wiped clean and dried, and a new pad placed in position. Almost 2 years of use proved the efficacy of the method.

Los Angeles. S. M. RABSON.

INCREASED ADRENOCORTICAL ACTIVITY AND MALIGNANT DISEASE

SIR,—We were interested to read the papers in your issue of Aug. 6 by Dr. Allott and Dr. Skelton and by Dr. Bagshawe concerning increased adrenocortical activity in association with malignant disease. It appears that in only one patient so far has increased aldosterone excretion been demonstrated.

We should like to add a further case recently seen in which a raised aldosterone excretion was associated with neoplasm of pancreatic islet tissue.

A 47-year-old male presented with œdema of the feet and mild generalised pigmentation. He subsequently developed diabetes mellitus but none of the other classical features of Cushing's syndrome. After the finding of hypochloræmic alkalosis and a serum-potassium of 1·5 mEq. per litre the aldosterone output was measured and found to be 16 μg. per 24 hours (upper limit of normal, 6 μg. per 24 hours; estimation by Dr. B. Singer, method of Neher and Wettstein 1956). His 17-ketosteroid excretion was 59 mg. per 24 hours and 17-hydroxycorticosteroid excretion was 134 mg. per 24 hours.

Death occurred within three months of the onset of the illness and was accelerated by the development of multiple abscesses, later found to contain a fungus. The primary growth was an islet-cell carcinoma of the pancreas. The adrenal glands were both enlarged but contained no secondary deposits.

Royal Hospital, Sheffield. P. C. FARRANT.

Children's Hospital, Birmingham. J. INSLEY.

ARTIFICIAL INSEMINATION

SIR,—In your leading article of July 30 you state "donor insemination and adultery are poles apart; but . . . as in adultery, the wife receives the seed of a man other than her husband". This surely is the theological argument against A.I.D. in a nutshell. The techniques may be new, but the theological attitude can hardly change with the times, as you hope, without cutting at the roots of Christian morality. The physical or emotional reactions of the woman concerned are beside the point, whether she commits adultery in the normal way, or whether she stifles her repugnance at receiving the spermatozoa of a total stranger by means of A.I.D.

To make my point clear, may I put it in another way? Like G. K. Chesterton, I find quite incomprehensible "Those who do not have the Faith, and will not have the fun". It comes to the same thing in the end.

Hale, Cheshire. AUDREY F. ROBERTS.

PAY INCREASE TO MEDICAL SUPERINTENDENTS

SIR,—The offer of more money for the medical superintendent is a retrograde move if it is designed to coax the best bedside (or couchside) psychiatric clinicians into the administrative office chair. Administration is not all that difficult and esoteric. The way of it—to satisfy the needs of the led—can be learned.

If medical administration there must be, then this should take the form of a shared consultative duty taken in rotation by senior medical colleagues for a few years at a time *without additional payment* as a social obligation. The offer of more money for the administrator at this time is paradoxical, as under the new Mental Health Act the medical superintendent will have less responsibility.

The Royal Commission contained business experts accustomed to be generous in the recognition of administrative service. Whether as an assessment of the value of the medical superintendents' added responsibility or as a "golden handshake" the extra £250 awarded can only be regarded as a derisory comment.

Luckily, the appointment of future medical superintendents is to become discretionary. Abolition of the post will bring back from the office into the wards and clinics at least a hundred badly needed full-time senior clinicians—a third of the total consultant psychiatric strength in the mental hospitals.

Deva Hospital, Chester. I. FROST.

EXTENSIVE VENOUS THROMBOSIS AFTER USE OF HYPERTONIC UREA

SIR,—In his letter of June 4, Mr. Small described local tissue necrosis following the use of hypertonic urea. Recently hypertonic urea was given to a patient undergoing a craniotomy for a cerebral tumour.

Before operation, the patient was comatose and had a right hemiplegia. There were few veins available but an intravenous infusion was started in the right foot where there was a reasonably good vein. After the dura had been reflected, an infusion of hypertonic urea was started. When 150 ml. had been run in, it was noticed that two veins proximal to the infusion site had become reddened. Soon the surrounding local area of skin became purplish and blotchy. The infusion of hypertonic urea was stopped and saline was injected through the needle. Within half an hour the whole leg and foot had become bluish.

The dorsalis pedis artery was palpable and remained so. It was obvious that an extensive spasm or thrombosis of the leg veins had occurred. The condition was treated with intra-arterial tolazoline and two lumbar sympathetic blocks with some improvement. The circulation slowly improved but on the following day the patient had a small pulmonary embolus.

As the swelling did not extend beyond the ankle, the right superficial femoral vein was explored. It contained a fresh clot. After opening it and removing the thrombus, satisfactory back flow was not obtained until an area probably as far proximal as the inferior vena cava had been cleared. The femoral vein was ligated. The patient's condition continued to improve during the next few days.

In this case there was no extravenous leakage of hypertonic urea, and there was a satisfactory reduction of intracranial pressure.

There have been reports of local venous thrombosis but it does seem worth reporting this case in view of the

possible severe consequences after the use of hypertonic urea.

In this case it would have been wiser to have prepared a cut-down and run the hypertonic urea into a bigger vein away from the extremities. I wish in no way to detract from the use of hypertonic urea, but to suggest that care be used in the choice of veins.

Department of Anæsthesia,
Saskatoon, Saskatchewan. A. McLEAN KEIL.

STAPHYLOCOCCAL DISEASE IN HOSPITALS

SIR,—There is one aspect of the epidemiology of staphylococcal disease in our hospitals which seems to have been overlooked—the physical climate in which the infection spreads from one subject to the next.

Before the advent of antibiotics, staphylococcal infection was responsible for many forms of disease in the humid tropics.[1] There was a wide range in the severity of these diseases. When the lesions were confined to the skin as in furunculosis or pyosis the mortality was negligible, but metastases in the viscera produced a very high mortality. The lasting impression made by a study of staphylococcal disease was that of an infection which particularly affected the skin and which was conveyed from one subject to another by direct contagion in a hot humid atmosphere. This impression was confirmed by observations particularly in passengers travelling by sea during the late war. Many doctors will remember how passengers had to huddle together in the living-rooms of ships under blackout restriction. In Lagos I saw the results of frequent epidemics of staphylococcal disease among passengers during the voyage out from home. I remember a family in which the father had otitis externa, the mother a breast abscess, and the infant boils and purulent blisters.

Most of these patients recovered quickly when they came ashore, but a few had to be sent to a hill-station or home to recover. Recovery was always accelerated in a cool climate.

The prevalence of bacillary dysentery and non-specific forms of enteritis in our hospitals again underlines the importance of climate in the epidemiology of hospital diseases. For purposes of prevention we should regard the staphylococcus as belonging to that group of infections which propagate best in a tropical atmosphere but which now flourish in the heat produced by the large expanse of glass in our wards in summer and by central heating in winter.

The nursing of patients in a cool climate used to be popular in the treatment of tuberculosis—often complicated by staphylococcal infection. There are therefore precedents both in home and tropical medicine for the introduction of " sanatorium regime " for the prevention and treatment of cross-infection in hospitals. The long-continued personal application of antiseptics by nurses, which has recently been recommended for the prevention of staphylococcal infection, cannot be a good thing, and the climatic approach to the control of staphylococcal disease might prove just as effective.

Bristol. WILLIAM HUGHES.

EPIDEMIC CERVICAL MYALGIA

SIR,—During the past four years in Mwanza my husband has suffered from repeated attacks of " stiff neck " and constitutional symptoms closely resembling those described by Dr. Davies in his account of epidemic cervical myalgia (June 11). The constitutional symptoms suggest that it is due to an infection. This view is supported by the fact that the man who brings our milk and our garden boy often ask for medicine for " pain in the neck ". I wonder whether others are familiar with this syndrome in this part of Africa or have any ideas as to its ætiology? If it is due to a virus, what is the nature of the recurrences? Virus infections are seldom chronic, and my husband had no attacks during five months in the United Kingdom last year. Repeated reinfection seems most likely; but why no immunity?

Mwanza, Tanganyika. MARGARET BENTON.

1. Hughes, W. *Quart. J. Med.* 1938, **7**, 537.

BRUXISM AND CHRONIC HEADACHE

SIR,—I have long believed that most chronic headaches without apparent cause are probably due to the formation of myalgic spots in the trapezius muscle and the deep muscles of the neck, causing, by local irritation of sensory nerves, referred pain to various parts of the head.[1]

In many longstanding cases secondary myalgic spots are found in the temporal and occipito-frontalis muscles—acutely tender on pressure—that resolve without local treatment once the primary spots in the neck have been successfully treated.

Very often, especially when the rheumatic process has spread and involved the insertion of the trapezius in its outer third at the occiput, these spots are found in the masseter muscles. They are usually quiescent, do not give rise to subjective symptoms, and are exceedingly tender on deep pressure. They may be activated by a number of causes such as trauma and dental and throat operations when the lower jaw has to be kept open often for a long period.[2]

In my view these myalgic spots would account for bruxism, described by Dr. Berlin and Mr. Dessner (Aug. 6), but this condition is secondary to rheumatism in the neck muscles. Teeth-clenching is quite a common habit in these days of tension and stress and should not give rise to any untoward symptoms in the absence of myalgic spots. In my view the wearing of a special dental plate is rather a grim alternative to the simple physiotherapeutic methods that can be adopted to relieve the myalgic spots.

London, W.1. LOUIS MOSS.

METALLIC TRACE ELEMENTS IN TOBACCO

SIR,—Inorganic analyses of fresh tobacco leaf have been confined almost entirely to the major constituents considered in relation to tobacco culture or plant physiology. The only published analyses of processed tobacco for metallic trace elements seem to be those of Tate and Whalley[3] which give semi-quantitative results from 261 tobaccos for manganese, lead, aluminium, barium, strontium, lithium, and sodium; and ratios of major ash constituents in an attempt to correlate ash composition and area of origin for Customs purposes.

Certain volatile inorganic constituents of processed tobacco may have been overlooked as possible carcinogens. Ionic inorganic constituents could also be involved in the incidence of oral cancer related to tobacco-chewing habit. Also, there may be a soil nexus in the relationship between the incidence of lung cancer and smoking. During the past thirty years a large proportion of tobacco smoked in Great Britain has come from " new " African sources.

Eleven samples of cigarettes and tobacco were purchased in the normal way from retail tobacconists. These were variously described as Virginia, Latakia, Mediterranean, and Empire, but unfortunately it was not possible to attribute to them definite location of source since these terms are really descriptive of tobacco type rather than geographical origin; moreover some will be blends. The primary objective was therefore to obtain data, unrelated to origin, for the trace-element concentration of tobacco by quantitative spectrochemical analysis. This could establish a range of concentrations for comparison

1. Moss, L. *Brit. med. J.* 1944, ii, 800.
2. Moss, L. *Med. Pr.* 1950, **223**, 515.
3. Tate, F. G. H., Whalley, H. K. *Analyst*, 1940, **65**, 587.

RANGE AND MEAN METALLIC ELEMENT CONTENT OF 11 SAMPLES OF TOBACCOS BOUGHT RETAIL

Element	Range	Mean
Manganese	69–184	135
Iron	300–1200	765
Cobalt	0·90–1·54	1·2
Nickel	3·58–11·00	6·2
Molybdenum	0·30–1·76	0·87
Titanium	85–270	188
Vanadium	Less than 0·15–6·10	2·3
Zinc	51–84	65
Tin	0·5–13·0	3·4
Lead	1·65–9·7 (34·5)*	5·3
Copper	23·2–168	65·7
Aluminium	800–3000	1350
Barium	24–170	105
Strontium	19–500	195
Lithium	9·3–56·4	32·1
Sodium	200–800 (2700)*	510
Magnesium	41×10^2–103×10^2	6780
Calcium	192×10^2–303×10^2	26,400

* Figure in parentheses well above range of others for this element, and not included for calculating mean.
All results in p.p.m. of dry matter, for 11 samples.
Calcium and magnesium, also sodium, are included for record because their proportions may be related to type of soil, especially if calcareous (as in many Mediterranean locations) or saline.

with other plant materials for which such data were already available. Cigarettes were analysed after removal of their paper.

The accompanying table gives the ranges and means of concentrations (excluding two very high figures) for all the elements determined.

Titanium contents are exceptionally high throughout. Comparable values for most Scottish crop plants and pasture species are from 1 to 4 p.p.m. In *Calluna vulgaris* (heather) values are higher and range mostly from 10 to 30 p.p.m. Total titanium contents of soil generally lie close to 1% so that the "apparent" titanium content of plant material can be taken as one of the most sensitive indicators of soil contamination.[4 5] By these standards, all the figures for titanium in the table suggest appreciable contamination with soil.

Iron and aluminium contents also were generally greater than what is normally encountered in clean plant material; and though the differences between soil and plant contents are broadly not quite so marked as for titanium, these high figures could also be accounted for by soil contamination.

Similar considerations apply to a varying extent to *vanadium*, *cobalt*, *nickel*, *strontium*, *barium*, *tin*, *lead*, and *lithium*.

The concentrations normally found in soils and plant materials of most of the other elements here recorded are more closely comparable, so that soil contamination has little effect on proportions of these elements in the plant material.

Manganese, *molybdenum*, *zinc*, *sodium*, *calcium*, and *magnesium* contents for tobacco are within the normal range found in most plant materials.

Lead in one sample is rather high although substantially lower than the figures given by Tate and Whalley.[3] This is the only element for which the two sets of results are not in agreement.

Copper contents are generally well above the range for Scottish crop plants; they include some exceptionally high figures. This could be explained by the use of agricultural sprays containing copper compounds or to contamination during processing.

The only conclusions or inferences that can be drawn from the results are:

1. These tobaccos contained abnormally high levels of a number of trace elements; the titanium content was exceptionally high.
2. The presence of high concentrations of some trace elements could be accounted for by soil contamination of the tobacco.

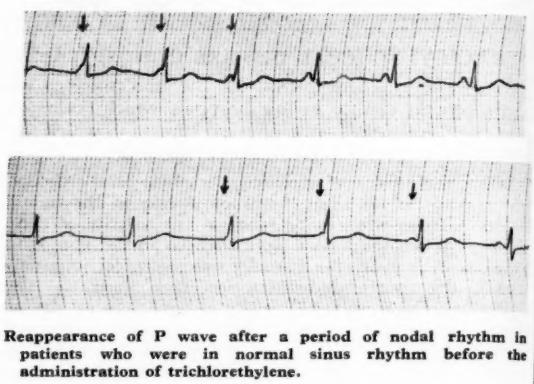
Listing the trace-element contents of a few samples of tobacco cannot of course in itself throw light on the problems involved in the relationship between cigarette smoking and lung-cancer incidence. Nevertheless, it can be suggested that attention might be paid to the possible role in this relationship of the inorganic constituents of tobacco, and to their relationship in turn to soil conditions.

West of Scotland Agricultural College, Auchincruive, Ayr. R. C. VOSS.
West of Scotland Agricultural College, Glasgow. HUGH NICOL.

4. Mitchell, R. L. Analyse des Plantes et Problèmes des Engrais Minéraux; p. 48. Institut de Recherches pour les Huiles et Oléagineux, Paris, 1954.
5. Calder, A. B., Voss, R. C. (*Scottish*) *Consultative Cttee Develop. Spectrogr. Work (Aberdeen) Bull.* 1957, no. 1, p. 32.

ELECTROCARDIOGRAPHIC CHANGES DURING ANÆSTHESIA

SIR,—Anæsthetists and others may be interested in the accompanying electrocardiograms, which were obtained from patients anæsthetised with trichlorethylene ('Trilene') after a thiopentone induction. They depict the change from atrioventricular (nodal) to sinoauricular



Reappearance of P wave after a period of nodal rhythm in patients who were in normal sinus rhythm before the administration of trichlorethylene.

(sinus) rhythm, with a phenomenon which may best be described as an "emerging" P wave, and which does not appear to have been recognised before.

One wonders whether the site of impulse formation in these patients has gradually travelled across the atrial wall from A.V. node to S.A. node over the course of three beats or so, or whether separate but almost synchronous impulses have originated in both nodes, with the S.A. node suppressing of the A.V. node as it asserts its own rhythm. Perhaps cardiologists could throw some light on the phenomenon.

Department of Anæsthesia, Chase Farm Hospital, Enfield. D. ZUCK.

TOBACCO MOSAIC VIRUS AND LUNG CANCER

SIR,—I wish to amplify my reference to the possibility of fragments of virus ribonucleic acid (R.N.A.) from tobacco mosaic virus (T.M.V.) passing over in tobacco smoke and to suggest experimental work which might uncover a possible relation between T.M.V. and lung cancer. Although access to the body would be quite possible by ingestion, the possibility of T.M.V. fragments, particularly R.N.A. (T.M.V.) fragments, passing via the smoke should not be discounted.

Viruses, however similar they may be in basic chemical constitution to normal constituents of cellular contents, often have the unfortunate property of causing cell disorganisation in the form of infection or neoplasia. Some viruses possess specificity (poliomyelitis, influenza, &c.) but in the case of the polyoma virus [1] the production of varying types of neoplasm is apparently associated with one virus, which might indicate that the ability to disorganise cell growth is not such a specific effect, or at least that one mechanism has slightly different effects in different cells.

The precise reasons for specificity are not certain, but there are grounds for accepting that the specificity for one disease or one group or reactions must be dependent on the nucleic-acid configuration, which also in turn probably determines the protein configuration of the virus. Some assistance in specificity may perhaps be given by the virus protein [2] and the final outcome will also depend on the result of interaction of the virus with the host.

1. Stewart, S. E., Eddy, B. E., Borgese, N. *J. Nat. Cancer Inst.* 1958, **20**, 1223.
2. Frankel-Conrad, H. *J. Amer. chem. Soc.* 1956, **78**, 882.

Viral specificity may essentially reside in the pattern of the nucleotide chain in the R.N.A. One nucleotide carries specificity but being a small molecule the information it carries is limited.[3] Benzer [4] has shown that in the phages the equivalent of only a few nucleotides are required to carry a unit of heredity—i.e., a gene marker. Similarly, in "transfer R.N.A." it seems likely that it is only a few nucleotides whose order determines both aminoacid reactivity and position of the R.N.A. in the ribosome.[5]

Todd [6] considerd that there must be a significant difference between the nucleic acids of the tumour cell and those of the normal cell. These differences, he considers, "will not be determined on the basis of gross analysis of the cellular nucleic acid preparations as we know them. The vital difference may be only in the base sequence of a few of the nucleic acids present (there must be many nucleic acids in the nucleus of the cell) or in the other possibility that . . . very small amounts of abnormal bases and nucleosides in many natural nucleic acids . . . may represent residues from nucleic acids of quite unusual structure present as very minor components of the nucleic acids examined"; and he asks whether these minor components could be more important in the economy of the cell. So there is nothing novel in suggesting that small parts of virus R.N.A. might be important. Hoyle [7] has suggested that in the case of the influenza virus the code might be in the host cell and the virus might only modify this code slightly (this in relation to a virus infection).

It is not, therefore, unreasonable to consider whether nucleotides, or nucleotide complexes derived from the nucleotides of the viral R.N.A. of T.M.V., could be implicated in the R.N.A. mechanism of the lung cell, and to consider whether being of viral origin they might be implicated in the economy of the cell in an important way. Clearly such an argument involves the preliminary assumption that the R.N.A. of T.M.V. is different (see the argument above) from the cellular R.N.A. of the lung and that the nucleotides or groups of nucleotides derived from it could continue to carry sufficient of the original viral R.N.A. pattern to be important.

It has been pointed out [8] that a good deal of R.N.A. fragments from other sources (food, tobacco leaf, &c.) would also be present in the gut and lung of the smoker, but this will not be of viral origin; viruses being viruses and food food, this will not matter. The question of which R.N.A.s are innocuous and which produce disease may be a question of the R.N.A. pattern specific to various species and we might well consider whether disruption or interruption of the R.N.A. mechanism of one species might occur more readily the further removed the type of R.N.A. "fed" to the cell is from that species. "Simple" viruses like the plant viruses may convey only restricted patterns in the R.N.A., or perhaps "confusion" or "limitation" patterns so far as the animal cell is concerned. Such simple viruses may also require assistance in penetrating animal cells.

Until the spatial configurations of the various R.N.A.s are accurately worked out, the answers to these problems will not be available; neither will the exact reasons for the difference between the effects of viral and cellular nucleic acid structures be known.

Since speculation should be followed by experimentation, it is worth setting out some of the questions to which answers are desirable in considering possible relationships between a plant virus (e.g., T.M.V.) and an animal disease (e.g., lung cancer in man).

Human Subject

1. What happens to T.M.V. in the body when it is ingested and inhaled (whole or in parts)?
2. Could it be demonstrated in lung tissue of smokers?
3. Could T.M.V. be demonstrated in lung-cancer cells if it was present?
4. Do smokers, or persons with lung cancer, have serologic evidence of antibody formation to T.M.V.?
5. Is it possible that the antibody formation could be localised and demonstrable in lung tissue particularly?

In a small series, 6 lung-cancer cases and 6 smokers were tested here, using a precipitin test with T.M.V. suspension against human sera: results were negative. This would, however, only concern protein reaction and perhaps complement-fixation test might be tried, although apparently doubt exists as to whether this would be more sensitive than precipitin tests for T.M.V.

Experimental Aspect

1. Does T.M.V. or do T.M.V. fractions confer any additional biological activity to tobacco tar?
2. If so, is this a function of the whole virus, fragments of it, or the nucleic acid.
3. Do tobaccos from differing sources represent different levels of virus content or different strains of T.M.V. virus—e.g. Virginia, Turkish, Rhodesian, &c.—and does tobacco drawn from these sources have more or less biological activity?
4. Are the biological effects (on skin cancer of animals) different in tobacco known to be infected with T.M.V. or otherwise?
5. What are the biological requirements for multiplication of T.M.V. in animal cells apart from intracellular localisation—i.e., are there factors in the oxygen/CO_2 balance and other metabolic characteristics which could make lung cells offer perhaps more closely these circumstances than other animal cells?
6. The behaviour of T.M.V. and other plant viruses introduced by micro-manipulation into animal cells might be of some value in establishing whether there are conditions in which this virus can exist in animal cells or at any rate what happens to them and the cell. Andrewes [9] suggested a manœuvre of this kind in relation to T.M.V. in plant cells.
7. The question has been asked whether R.N.A. viruses might behave differently in different hosts.[10] This would appear to be worth follow-up, since a virus which multiplies in a plant cell might have a more restricted (but important) role in the animal cell.

I am well aware that the views I have expressed on the possible relationship between a plant virus and animal disease are highly speculative and until some work is done on the subject only further speculation can be added; and also that such speculation involved the setting up of "biological bridges" for whose existence there is only fragmentary evidence at present. But this does not mean that the possible existence of such bridges between the plant virus and animal cells should not be sought or that those who seek to build them or suggest experimentation towards that end are alchemists.

Bristol. P. W. BOTHWELL.

3. Zamenhof, S. The Chemistry of Heredity; p. 31. Oxford, 1959.
4. Benzer, S. *in* The Chemical Basis of Heredity (edited by W. D. McElroy and B. Glass). Baltimore, 1957.
5. Hoagland, M. B. *Scientific American*, Dec. 1959, **201**, 6, 59.
6. Todd, A. *Brit. med. J.* 1959, ii, 517.
7. Hoyle, L. The Nature of Viruses. Ciba Foundation Symposium, 1959; p. 117.
8. Pirie, N. W. *Lancet*, 1960, i, 978.
9. Andrewes, C. H. The Nature of Viruses. Ciba Foundation Symposium, 1959; p. 280.
10. Isaacs, A. *ibid.* p. 281.

LONG-ACTING INTRAMUSCULAR STEROID

SIR,—Patients requiring long-term oral steroid therapy may develop side-effects which necessitate careful supervision to assess clinical progress and to enable the physician frequently to adjust the dose so that the maximum of clinical benefit is obtained, with the minimum of undesirable complications. Not infrequently, patients are too casual about their treatment or tend to forget to renew their tablets, with all the dangers this entails. A short clinical investigation of a long-acting intramuscular preparation of 6-α-methylprednisolone ('Depo-Medrone') has been carried out in this hospital over the past six months to discover whether patients, falling into the above group, could advantageously be transferred from oral to intramuscular treatment, thus allowing closer supervision and ensuring that the patients actually received the dose intended.

The patients had all previously had oral medication and were being kept symptom-free by long-term therapy. There were 5 cases of senile dermatitis herpetiformis, 2 of exfoliative dermatitis, 1 of acute lupus erythematosus, and 1 of pemphigus vulgaris. The dose was given weekly by a single intramuscular injection calculated as follows:

The oral daily requirement of steroid, expressed as methyl-

prednisolone (25 mg. cortisone = 20 mg. hydrocortisone = 5 mg. prednisone or prednisolone = 4 mg. methylprednisolone), was multiplied by seven, thus giving in mg. the total weekly dose required. A simple conversion to ml. was then made (1 ml. depo-medrone contains 40 mg. 6-α-methylprednisolone).

Before substituting the long-acting drug, liver-function tests, serum-electrolytes, E.C.G.s, and X-ray examination of the chest were checked, and these tests were repeated after four and eight weeks. None showed any material changes.

With the exception of one patient with senile dermatitis herpetiformis, who relapsed, all patients maintained the clinical improvement obtained on oral therapy and so far none has shown sign of relapse. It has been possible in four of them to lower the total dose required, suggesting that where one tablet daily is insufficient, and two tablets daily is too much, the intramuscular preparation may be advantageous in that the total weekly dose of steroid can be more easily adjusted than by giving numbers of tablets of differing strength to achieve exact maintenance levels.

We have also given depo-medrone intradermally into resistant lesions of chronic conditions such as chronic lupus erythmatosus, lichen simplex, lichen planus, &c. Five such cases were treated with benefit.

It seems that a long-acting intramuscular preparation, such as 6-α-methylprednisolone can be an adequate substitute for oral steroid therapy in patients who, because of side-effects or carelessness, require close supervision of their therapy and that benefit can especially result in those patients who develop gastric intolerance.

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J. O'D. ALEXANDER
GEORGE HARVEY.

FEMALE PSEUDOHERMAPHRODITISM DUE TO PROGESTOGENS

SIR,—Reports describing masculinisation of the female fœtus by progestogens administered to the mother have appeared in recent years.[1–7] Ethisterone (17-α-ethynyl testosterone), norethisterone (17-α-ethynyl 19-nortestosterone), norethynodrel, and progesterone have all been held responsible. Grumbach et al.[6] considered that œstrogens, which are often given concurrently, may be a contributory factor. Coincident virilisation of the mother has been noted in a few cases but has been mild and temporary.

I describe here two further cases, due to norethisterone, a drug which is variably stated to have an androgenic effect $^1/_{12}$ to $^1/_5$ that of methyl testosterone, although some believe it has no such effect at all.

CASE 1.—Birthweight 5 lb. 2 oz. This baby was born at 36 weeks by spontaneous breech delivery and was brought to the premature-baby follow-up clinic for a routine visit at the age of three weeks, The mother was worried about the size of the child's clitoris, which she said had been large from birth. The abnormality had not, however, been sufficient to cause difficulty with regard to determination of her sex.

The clitoris was indeed large, as were the labia, which were separate and did not contain palpable gonads. The urethral orifice was not seen, but urine seemed to appear at what was taken to be a small vaginal orifice behind the base of the phallus.

Apart from moderate breast enlargement there were no other abnormalities and the general condition was and had been good.

The pregnancy had been uneventful, but because of a past history of spontaneous abortions the mother had been given hormone therapy from the 11th to the 34th week (ethinyl-œstradiol 0·1 mg. b.d., total 64·9 mg.; norethisterone 10 mg. b.d., total 3100 mg.). The baby was admitted to Chase Farm Hospital under the care of Dr. C. Allan Birch, where it was found that the urinary steroid excretion was within normal limits (Mr. R. Smith): 17-hydroxycorticosteroids 0·78 mg. in 24 hr., 17-ketosteroids 0·72 mg. in 24 hr.

She was then transferred to the North Middlesex Hospital under the care of Dr. Ian Wickes. It was found that the blood chemistry was normal and the chromatin pattern (buccal smear and blood-film) was of the female type (Dr. Ian Gordon). Examination under anæsthetic by Mr. B. H. Page showed that the vagina opened into the posterior wall of the urethra and a cystoscope along this revealed a normal bladder.

The good general progress continued, but the breasts remained large for many weeks, and at 10 weeks there was an episode of vaginal bleeding which ceased spontaneously. The clitoris was gradually becoming smaller, but was not yet normal at this time.

CASE 2.—Birthweight 8 lb. 6 oz. This baby was delivered normally at full term at Chase Farm Hospital. From the start there was doubt about the child's sex and she was originally registered as a male.

The clitoris was enlarged and the labia were large and scrotal, slightly fused at the posterior ends but not containing palpable gonads. Behind the base of the clitoris was a small orifice from which urine appeared.

The mother had received steroids from the 8th to the 35th week on account of two episodes of vaginal bleeding during the pregnancy: ethinylœstradiol (0·05 mg. b.d., total 19·1 mg.), norethisterone (10 mg. b.d., total 3715 mg.). The general condition of this baby was good and she was transferred to the care of Dr. Wickes for investigation. Urinary 17-ketosteroids 0·08 mg. in 24 hr. (Miss B. E. W. Vage). Chromatin pattern (buccal and blood-smears) female (Dr. Gordon). Examination under anæsthetic (Mr. Page): a cystoscope passed into the opening in the perineum passed anteriorly to a normal bladder, the vagina opening into the posterior wall of the urethra. No cervix was seen.

Progress was good but interrupted at 10 weeks by a mild vaginal bleeding. It was noted at this age that the breasts were enlarged and the nipples pigmented. By 14 weeks the clitoris had regressed to almost normal size.

In pseudohermaphroditism due to these steroids the anatomical changes are limited to the external genitalia and are non-progressive. The degree of abnormality varies and appears to be related to the time of onset of therapy.[6] Enlargement of the clitoris is invariable but may be of such a slight degree as to be overlooked at birth; spontaneous regression is usual. The labia majora are often large and rugose and may be fused to a variable degree. The vagina and urethra may open separately on to the perineum or a urogenital sinus may persist. This may open on the perineum where it is usually partly obscured by the fused labia, or it may be enclosed to form a phallic urethra. The chromatin sex is always female, the adrenal function is normal, and normal uterus, tubes, and ovaries are present. In the more severe cases some difficulty has been encountered in determining the sex at birth.

It is interesting that both our cases showed gynæcomastia and vaginal bleeding occurring at the tenth week. These same features occurred in Valentine's case, also at 10 weeks of age, but have not been described by other writers. We felt that this could be explained by a rebound overactivity of the pituitary gland, following intrauterine suppression by the steroids given to the mother.

Although these steroids are widely used in pregnancy for cases of habitual or threatened abortion it must be admitted that pseudohermaphroditism due to them is rare. The purpose of publishing these cases is, however,

1. Wilkins, L., Jones, H. W., Holman, G. H., Stampfel, R. S. *J. clin. Endocrin.* 1958, **18**, 559.
2. Moncrieff, A. *Lancet*, 1958, ii, 267.
3. Hayles, A. B., Nolan R. G. *Proc. Mayo Clin.* 1958, **33**, 200.
4. Grossman, M. (quoted by Reilly, W. A., et al.) *Amer. J. Dis. Child.* 1958, **95**, 9.
5. Jolly, H. *Proc. R. Soc. Med.* 1959, **52**, 301.
6. Grumbach, M. M., Ducharme, J. R., Moloshek, R. E. *J. clin. Endocrin.* 1959, **19**, 1369.
7. Valentine, G. H. *Arch. Dis. Child.* 1959, **34**, 495.

to draw attention to the condition and to suggest that the drugs are used with discretion.

I wish to thank Dr. Ian G. Wickes and Dr. C. Allan Birch for permission to publish these cases and for their help, and Dr. D. Ferriman, of the North Middlesex Hospital, for his help and criticism.

Queen Elizabeth Hospital for Children, London, E.2. P. E. MORTIMER.

DIRECT INHIBITION OF HEPATIC GLYCOGENOLYSIS BY TOLBUTAMIDE

SIR,—The action of oral antidiabetics on the liver is not yet clearly understood. Several facts seem to indicate "direct" hepatic effect, but the liberation of small quantities of endogenous insulin into the portal system has also been postulated.[1] To study this possibility, glucose production in rat's liver has been determined by artificial perfusion using the method of Issekutz.[2]

Livers from male albino rats, weighing 120–150 g., which had been starved for 24 hours, were used. The livers were removed and cannulas were inserted into the portal vein. After rinsing with 20–50 ml. glucose-free Tyrode solution (38°C), they were perfused with 100 ml. glucose-free Tyrode solution containing 100 mg. tolbutamide. The fluid collected was passed through a closed system into a tank, so that a fairly constant circulation was established. The glucose content of the perfusion fluid was determined after one and two hours by the Hagedorn-Jensen method. The results of six experiments with tolbutamide and six controls receiving only glucose-free Tyrode solution are shown in the table.

GLUCOSE RELEASE IN RAT'S LIVER DURING PERFUSION WITH GLUCOSE-FREE TYRODE SOLUTION AND WITH TOLBUTAMIDE IN GLUCOSE-FREE TYRODE

—	Glucose release (mg. glucose per g. liver per hour)			
	Glucose-free Tyrode		Glucose-free Tyrode plus tolbutamide (100 mg. per 100 ml.)	
	1 1st hour	2 2nd hour	3 1st hour	4 2nd hour
	16·3	9·3	8·6	−5·5
	10·3	6·8	2·1	1·4
	9·1	3·1	2·4	−0·3
	18·4	3·7	9·5	0·8
	14·7	6·9	5·9	0·3
	9·5	1·3	3·3	−0·6
No. of cases ..	6	6	6	6
Mean	13·1	5·2	5·3	−0·7
Standard deviation ..	±3·5	±3·0	±3·2	±1·9

Significant decrease between column 1 and column 3 ($t=4·02$, $P<0·01$) and between column 2 and column 4 ($t=3·73$, $P<0·01$).

A significant decrease in glucose release was observed after tolbutamide, and this change was more pronounced after the first hour of perfusion. In these experiments the possibility of insulin action may be practically excluded, so the "direct" effect of tolbutamide upon the liver seems apparent. Investigations concerning the role of others drugs are in progress.

2nd Department of Medicine, University of Budapest. ANTAL KÁLDOR GÁBOR POGÁTSA.

TUBERCULIN TESTING OF DOCTORS

SIR,—During the past two months I have seen three young medical men, one with a tuberculous pleural effusion and two with tuberculous adenitis. Two of these men qualified abroad and one in London. None of the three had been tuberculin-tested as a student and only one, who had been a house-physician at a chest hospital, had been tuberculin-tested before taking up a resident appointment.

I have also seen, during the same period of time, two medical students suffering with tuberculous pleural effusions; both are studying in London, one in his last year and the other about to begin his clinical studies. Neither of these men had a tuberculin test done before the onset of his illness.

Whilst it is easy to understand how the occasional student may be missed when the routine tuberculin-testing is done, the results of such an omission may well be serious to the individual concerned, and every care should be taken to follow up the defaulters. It might also be wise if every consultant were to assure himself that his new houseman was tuberculin-positive before allowing him to work on wards where he might be exposed to infection.

Pinewood Hospital, Wokingham, Berkshire. JOHN J. MCCANN.

SERUM-ALDOLASE AND SERUM-TRANSAMINASES IN TRICHINOSIS

SIR,—It is well known that in diseases involving tissue damage some tissues enzyme are liberated from the cells and their activity greatly increases in the serum. Many workers have described the rise in serum-glutamylo-pyruvic-transaminase (S.G.P.T.) and serum-glutamylo-oxalaocetic-transaminase (S.G.O.T.) in infectious hepatitis, cirrhosis, coronary thrombosis, hæmorrhagic pancreatitis, and malignant neoplasm,[1–4] Serum-aldolase (S.A.) is elevated in infectious hepatitis, malignant neoplasm, coronary thrombosis, and progressive muscular dystrophy[5–7]; but the activities of these enzymes in trichinosis has not been mentioned.

In our department we have observed 30 patients with trichinosis (18 females and 12 males). We diagnosed mild trichinosis in 12 cases, intermediate in 12, and severe trichinosis in 6 cases. All patients recovered without complications.

We have determined the activity of aldolase in the sera of these patients, using the method of Bruns and Puls,[5] and the activity of transaminases using the method of Umbreit et al.[8]

The activity of these enzymes increased gradually in all patients at the beginning of the illness and was highest during the fourth week. Thereafter activity diminished and the normal values were restored by the seventh week.

In mild trichinosis aldolase activity increased on the average to four times normal and transaminases activity to twice.

Intermediate cases showed higher activity of transaminases (S.G.O.T. increased four times, and S.G.P.T. five times) and an important elevation of S.A., which increased ten times during the fourth week of disease.

In severe cases the activity of all enzymes increased from the beginning of the disease. Maximal values were reached in the fourth week (the increase in aldolase was especially great). Thereafter activity fell rather slowly.

The increase of enzyme activity can be explained by increased liberation of enzymes from the skeletal muscle cells. The damage to these cells, due to the invasion of parasites, reaches its peak in the fourth week of disease. The activity of the enzymes in the serum seems proportional to the extent of muscle damage in trichinosis. It is possible, therefore, that study of aldolase and transaminases may be useful for diagnosis and for evaluating the course of trichinosis.

A. MALIK
S. NIEWIAROWSKI
K. RACHON.

I Clinic of Infectious Diseases, Medical School, Warsaw.

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2. Issekutz, B. *Biochem. Z.* 1924, **147**, 264.
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3. Chinsky, M., Wolff, R. J., Sherry, S. *Amer. J. med. Sci.* 1957, **233**, 400.
4. Wroblewski, F. *Amer. J. Med.* 1959, **27**, 911.
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7. Sibley, J. A. *ibid.* p. 339.
8. Umbreit, W. W., Kingsley, G. R., Schaffert, R. R., Siplet, H. *J. Lab. clin. Med.* 1957, **49**, 455.

ETHER AND CAMPHOR IN THE TREATMENT OF WHOOPING-COUGH

SIR,—In 1951 I observed the striking effect of ether in two children suffering from whooping-cough who were anæsthetised after an accident. Later I learned that the reduction of the severity of whooping-cough by ether had been observed more than twenty years earlier. I started recording the treatment of whooping-cough by different drugs, and the results were as follows:

(1) 52 patients with uncomplicated whooping-cough were treated with tetracycline for ten days. The result was good in 7 patients, slight in 18 patients, and the rest showed very little improvement.

(2) 30 patients were treated with chloramphenicol and the result was promising in 8. Slight improvement was seen in another 7 patients, in 1 of whom the drug was stopped because of blood dyscrasia. In the others the parents reported complete failure. They were all uncomplicated cases and were all limited to ten days' treatment.

(3) 179 patients with uncomplicated whooping-cough were given injections of anæsthetic ether. From 1 to 2·5 ml. was injected subcutaneously or (preferably) intramuscularly daily or twice a day. The result was outstanding. More than 60 patients claimed improvement from the first injection. They slept better, the number of the spasms was less, and their severity decreased. Within eight days of treatment with ether more than 80% showed great improvement.

(4) 9 patients were treated with spiramycin, which seems to be more valuable than the other antibiotics but far less effective than ether.

(5) 19 patients were treated by a wholly new method: gr. 1–4 of camphor were injected subcutaneously and there was definite improvement in all cases.

(6) 25 patients were given ether and camphor in one injection, and 20 improved dramatically.

Of 21 patients with complicated whooping-cough (mostly with pneumonia), 11 were given tetracycline and 10 tetracycline plus injections of ether and camphor. In the 11 on tetracycline alone, the complications rapidly subsided but the whooping-cough took its usual course. In the other 10 both the complications and the whooping-cough started to improve rapidly.

With ether and camphor injections the whooping-cough subsided much more quickly than with any other method.

It has been said that injections of ether are very painful, but I tried them myself and found it much less painful than quinine, nikethamide, vitamin C, or phenobarbitone.

Omdurman, Sudan. B. A. G. KHALIL.

IMMUNOELECTROPHORETIC IDENTIFICATION OF β-MYELOMA PROTEIN IN NEOPLASTIC PLASMA CELLS

SIR,—The production of γ-globulin by neoplastic plasma cells was established by Serre et al.[1] in a case of γ-myeloma, thus furnishing direct proof. No similar data are known concerning β-globulins. We have succeeded in demonstrating β-myeloma protein in the pathologically increased plasma cells in two cases of β-myeloma.

Bone-marrow was taken postmortem from ribs, vertebræ, and femur in one instance, and by aspiration from the iliac crest in vivo in the other. Cytological examination revealed in both that the marrow contained almost exclusively plasma cells. The marrow was repeatedly washed with physiological saline till no protein could be detected in the washings, either by 20% trichloracetic acid precipitation or immunoelectrophoresis. After washing the marrow cells free from plasma, they were homogenised in a Potter homogeniser. The homogenate was centrifugated at high speed, and the supernatant was investigated by immunoelectrophoresis, using the patient's sera as control (according to the method of Scheidegger,[2] anti-human rabbit serum serving as antibody).

In both cases there was one single precipitate observable, the localisation of which corresponded to that of the pathological β-globulin fraction derived from the sera. It can thus be concluded that in these two cases the only protein fraction immunoelectrophoretically demonstrable in plasma-cell homogenate is identical with the β-myeloma protein.

3rd Department of Medicine, University of Budapest. J. GERGELY G. SZINAY.

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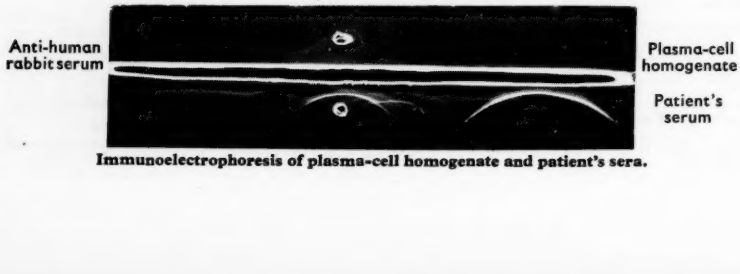


Immunoelectrophoresis of plasma-cell homogenate and patient's sera.

ASTHMATIC CHILDREN TAKE THE WATERS

SIR,—Your readers may like to know of arrangements whereby asthmatic children of 5–15 can be treated at La Bourboule, a French spa which specialises in the treatment of allergic disorders. For more than ten years small parties, organised and subsidised by International Help for Children, have been visiting La Bourboule; and recently I accompanied one of them.

La Bourboule is a small town in the heart of the Auvergne, 2765 feet above sea level. Its water is hot (60°C) and contains arsenic (0·00705 g. per litre). Experiments in the spa laboratory suggest that the water has an adrenaline-like action on bronchial muscle; but they seem to be done without adequate controls.

A course of treatment lasts three weeks, and the English children receive favourable terms. The doctors and the company owning the spa provide free treatment for special cases, and in practice more than half the English children are treated free. Some of the doctors charge no fee at all for treating these children. The usual charges are also reduced by Skyways, who fly the parties out, and by the homes where the children stay. The full cost of the trip is thus about £60 per child. Parents contribute whatever they can afford, usually about £20–£30. Few pay the full amount, and some pay nothing. The difference, about £700 a year, is paid by International Help for Children, who raise it through appeals in the Press and through private generosity.

The children stay in special children's pensions whose carefully regulated regimes include several hours' rest each day. Soon after arrival each child is examined by a doctor, who prescribes individual treatment and arranges further appointments. Free time is spent playing in the "children's park" and walking in the mountains.

Treatment is carried out at the thermal establishment, to which the children are taken every morning. It consists in application of the waters of La Bourboule in various ways and to various parts of the body. There are slipper baths, steam rooms and douches, and many kinds of apparatus which vaporise the waters for inhalation. Like most British doctors, I was brought up to be rather sceptical of the value of spa treatment; but on the whole I was very favourably

2. Scheidegger, J. J. *Int. Arch. Allergy*, 1955, **7**, 103.

impressed with what I saw. I am certain that La Bourboule has "got something", though exactly what it has is hard to say.

All the children who travel in these parties are recommended by, or at least have the approval of, their family doctor. Their doctors' reports are kept by International Help for Children along with the reports of the children's parents. Some months after the treatment a follow-up questionnaire is sent, which elicits almost 100% return.

Many of the children suffer from intractable and disabling asthma, and often eczema too. Doctors treating them at home have often reached a therapeutic impasse and are waiting and hoping for the children to "grow out of it". Meanwhile the children are missing many months of schooling every winter, often becoming increasingly deformed in both mind and body—and more and more firmly tied to their mothers' apron-strings.

The following results are taken from the records for the past ten years:

CONDITION OF ASTHMATIC CHILDREN AFTER VISIT

Condition at follow-up	Boys (100)	Girls (72)
Definitely improved	85%	82%
No change	14%	15%
Worse	1%	3%

Most of the favourable reports are backed up by remarks such as "more confident", "less nervous", "only missed 4 days school last winter instead of the usual 4 months" or (parent quoting child's own request) "Throw away the pills, Mummy; I've been to France and I'm cured now".

A visit to La Bourboule seems to break the vicious circle. The child is taken away from home, visits a new country, and receives concentrated treatment in an optimistic atmosphere. It is assumed that he will get better. He usually does. Such asthmatic attacks as did occur during the visit were sensibly managed and swiftly ended, usually without the use of drugs other than aminophylline (which is widely used by the French doctors). I was also fascinated to watch a dermatologist treating a stunted asthmatic child whose severe eczema covered most of his body. This doctor treated the child by means of the *douche filiforme*, a fine jet of hot spa water delivered at very high pressure with the aid of complicated manual movements, which he assured me acted as massage. After several days the eczema had virtually disappeared, at least temporarily.

It may be that the waters of La Bourboule exert a permanent beneficial influence in allergic disorders. It may be that the results are good partly because the apparatus is so impressive; I agree that the equipment for nebulisation (vapours), pulverisation (aerosols), nasal douching, gargling, and bathing is so impressive that no patient could doubt is efficiency.[1] A noted pædiatrician has been heard to remark that the best way of treating asthma is to provide a "therapeutic orphanage": it may be that this plays an important part in the success of La Bourboule, though it should be pointed out that many French children come for treatment with their mothers (who are often treated too!). But certainly the English children, who were sent with long lists of written maternal regulations about food, sleep, tablets, warm clothes, and bowels, appeared to derive great benefit from the freedom resulting from everyone ignoring these instructions.

It may be that the success of La Bourboule comes also from its delightful situation, its mountain walks, and the increase of appetite that comes from leading a healthy life. I suspect that the improvement is also due in no small part to the energy, interest, and devotion shown by the organisers of International Help for Children. I feel sure that the tremendous personal interest they take in each child has a big, and probably lasting, effect.

Whatever the cause of the success, and whatever our opinion of spa waters, there is certainly no "therapeutic establishment" in Britain where we can send asthmatic children away from their families and give them intensive and purposive treatment in beautiful surroundings with mountain walks and with a large number of admirable people determined to help them.

Anyone who has a patient who might benefit from a visit to La Bourboule can write to International Help for Children, 43, Parliament Street, London, S.W.1.

1. *Lancet*, 1949, ii, 1187.

London, S.E.21. ANN MULLINS.

CARCINOGENICITY OF IRON-DEXTRAN COMPLEX

SIR,—Respect must be paid to the views and experience of Dr. Duthie and his co-signatories, expressed in their letter of July 16. Meantime I have had the advantage of some correspondence with them. It is obvious and accepted that the administration of a great many drugs in common use is a calculated risk, when the hope or certainty of immediate benefit has to be weighed against the possibility of later toxic effects. But I have been specially impressed by various considerations they have raised in the particular case of 'Imferon': for example, that many patients correctly so treated have disease of the alimentary tract reducing their life expectancy to below a latent period within which any carcinogenic hazard is improbable; or, secondly, that no advantage is to be achieved in withholding imferon from patients with unquestionably refractory iron-deficiency anæmia, if they are left without effective treatment, or given therapy carrying an immediate and known hazard, as from intravenous iron or transfusions.

Having said this, I am, however, quite certain that no-one is justified in asserting at the present moment, as the authors do, that the use of imferon in the clinical dosage recommended carries a negligible risk. From the nature of the case we cannot have a useful answer to this question under something of the order of 15–20 years. The statistics of the hazard (if indeed it exists in man) are quite unknown. We cannot therefore say it is negligible.

The letter also raises another question. If the results of experimental work with imferon are in practice to be disregarded as an indication towards policy in man, what evidence from experimental work would be acceptable as justifying either the prudent withdrawal of a given preparation, or at least a warning statement? Although the results of animal experimentation are immensely valuable in this kind of problem, they can never be regarded as more than an approximate guide. Agreed that we cannot extrapolate with any certainty to man, it will also be agreed that had the results of animal experimentation with imferon been negative, they would certainly (and not unreasonably) have been used as indicative of the preparation's harmlessness.

On balance, I believe all the work on imferon originating from H. G. Richmond's most interesting observation, and extended in other papers and correspondence, has been profitable. It appears that the preparation had been used in very many cases without adequate indication, or indeed almost indiscriminately; and a useful result may be considerably to reduce its administration to younger age-groups, and to patients capable of responding perfectly satisfactorily to other means.

Chester Beatty Research Institute, London, S.W.3. ALEXANDER HADDOW.

—— IS GOOD FOR YOU

SIR,—Correspondence flares up periodically in the medical press the main theme of which goes somethng like this: "Why do the pharmaceutical manufacturers waste these vast sums of money on expensive circulars we throw straight in the w.p.b. and pages of advertisements in the journals we never read?" One is reminded of the old story of the man who claimed that he, at any rate, was unaffected by advertisements. "Take Guinness, for instance," he said, "I don't drink it because it's advertised. I drink it because I know it's good for me."

London, W.C.1. A. S. O'CONNOR.

THE OVERWORKED E.S.R.

SIR,—May I put in a plea for the much overworked erythrocyte-sedimentation rate (E.S.R.)? It is such a valuable test when properly used; if used indiscriminately in such conditions as pregnancy, pyrexia, anæmia, &c., not only is the result valueless, but, if taken seriously, may be positively misleading. The most recent example of misuse was when the E.S.R. was asked for in an eight months' pregnant pyrexial woman to "find out why she was passing blood in her urine".

Department of Pathology,
Kent and Canterbury Hospital,
Canterbury. I. B. MORRIS.

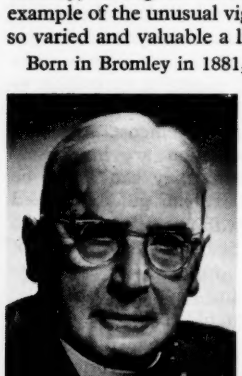
Obituary

FRANK GARFIELD HODDER WILLIAMS

O.B.E., M.B. Lond., LL.D. Manc.

As we recorded last week, the Very Rev. Garfield Williams, Dean Emeritus of Manchester since 1948, died on Aug. 8. He had lately returned from the United States, where latterly he had spent part of each year working in the diocese of Central New York. His appointment, in 1950, as canon in an American diocese was an unusual honour, while his enjoyment of new work in another country, during his seventh and eighth decades, was an example of the unusual vigour and devotion that gave him so varied and valuable a life.

Born in Bromley in 1881, he was the grandson of Matthew Hodder, founder of the publishing firm of Hodder & Stoughton, and great-nephew of Sir George Williams, founder of the Young Men's Christian Association. From the City of London School he went to St. Bartholomew's Hospital, and he qualified in 1908; but already he wanted to undertake Christian service in which medical work would be secondary. Before going to India in 1908 he had visited China, Japan, and the United States, and been London secretary of the Student Christian Movement. Representing the S.C.M. in Calcutta, he was (*The Times* says) "one of the first British observers to draw widespread attention to the depressing, unhygienic, and, in some ways, demoralizing conditions of non-residential collegiate student life" in that city.



After four years as vice-principal and superintendent of the science department of St. John's College, Agra, he was ordained in 1914 and spent the next few years as principal of St. Andrew's College, Gorakhpur, being elected a fellow of Allahabad University in 1917. Towards the end of the war he was asked to edit the sole organ of Government publicity in the United Provinces, and in 1919 he was appointed O.B.E.

His Indian period ended in 1920. After a short time as a science master at Rugby School, he became foreign secretary of the Church Missionary Society, in charge of education. For five years from 1924 he was secretary of the Missionary Council of the National Church Assembly, and edited the *World Call Reports*, besides reports on educational and missionary problems in India and Africa. His books included *What If He Came?* (a meditation on the gospel of St. Mark) and *Personal Questionings*.

In 1927 Dr. Garfield Williams became an honorary canon of St. Albans, and in 1929 he was appointed Dean of Llandaff. Here he showed himself a liberal as well as a vigorous Churchman, on friendly terms with Welsh Nonconformists. After little more than eighteen months he was recommended to Manchester, where he was Dean from 1931 to 1948.

Canon Peter Green, in an appreciation published in *The Guardian* of Aug. 10, said that the expressions "team work" and "team spirit" really did express his mind and method of working. With great powers of organisation, "he possessed to a remarkable degree the power of drawing out the best of men with whom he worked", driving and directing a great team "with a very light but quite firm hand on the reins" As a speaker or preacher he had a capacity of rising to the call of a great subject or a great opportunity.

H. P., who knew him in Manchester as a hospital governor, as Dean of the cathedral, and on occasion as patient, writes: "It was an old tradition that the Dean of Manchester was a member of the committee of management of the Royal Infirmary. In this capacity Garfield Williams contributed not only his wisdom in general affairs, but his understanding of the needs and aspirations of the medical staff. As regards his knowledge of medicine, he always insisted that he had forgotten most of what he had learned as a student! Nevertheless, he took pride in the fact that he was a 'Bart's man', and that those years had been a unique preparation for his missions in India . . . He was a big man in every sense, and Medicine can rejoice that it helped him to find his true vocation in the Church."

In December, 1940, the ancient cathedral of Manchester was severely damaged by bombing—more severely than any other British cathedral except Coventry and perhaps Llandaff. The Dean's courage and leadership after the bombing were an inspiration to the citizens of Manchester—recalled in *The Times* of Aug. 12 in a friend's tribute to the vision and energy with which, in the next eight years, he organised the work of reconstruction.

When, for reasons of health, he had to retire from Manchester, and went to live in North Devon, he gave much time and thought to the development of hospitals under the National Health Service in the South Western region, being at one time chairman of a regional committee on medical research.

Dr. Garfield Williams was a man whose enthusiasm and earnestness were infectious, alike in his sermons and in everyday affairs. At the same time he was both shrewd and tolerant—an experienced observer and valuable adviser. As the years passed, the personal shyness of the preacher and idealist was forgotten in his equally personal wish to help other people, which he continued to do very actively till the last day of his long life.

Mrs. Garfield Williams is a daughter of the Rev. Thomas Nicholson. Their son, Mr. Paul Hodder-Williams, has, like his father, been for many years a member of the board of directors of *The Lancet*, as well as of his great-grandfather's publishing firm.

DEAN ABBOTT SMITH

O.B.E., M.D. Cantab., D.T.M. & H.

DEAN of the faculty of medicine and professor of physiology in the University of Khartoum, Dr. Dean Smith made, in a very few years, a deep impression on medical teaching in the Sudan and on the spirit and atmosphere of the medical faculty. He died in this country on July 27 at the age of 50.

Educated at Uppingham, Sidney Sussex College, and St. Mary's Hospital, he qualified in 1933, and two years later went to Hong Kong in the Colonial Medical Service. He was badly wounded when the Japanese attacked the island, and he and his wife were interned for over three years. His work in Stanley Camp included the hard task of nutrition officer, and he became familiar with many forms of malnutrition. For the aid and encouragement he gave to prisoners by his work and his example, he was appointed O.B.E. After the war he continued to give much time to questions of nutrition, and he was joint author of *Deficiency Diseases in Japanese Prison Camps*, a report for the Medical Research Council which appeared in 1951.

A physiological colleague writes of Smith's wartime achievements and of his years in the Sudan:

"Dean Smith was one of the most energetic people I ever met—medium height, well-built, with great powers of endurance. His left elbow was seriously damaged by a Japanese shell in 1942, and during years of internment he must have been greatly hampered by what he always referred to as his 'silly' arm, and also eventually by the burden of beriberi. But despite these handicaps, in the middle of other medical duties, he was in charge of camp rations and kept minute records (no doubt at considerable risk) which he brought safely home to provide the basis for the memorable M.R.C. Special Report no. 274 (written with Prof. M. F. A. Woodruff), and also for his M.D. thesis. Because of his injured arm, he was carried into the internment camp on a stretcher, and this allowed him to smuggle in a considerable amount of vitamin B_1, which must have been a godsend to the prisoners. Another example of his prescience was the regular abstraction during the years of internment of a tiny fraction of the rations to accumulate a store against the day when the Japs would be defeated and would desert the camp, leaving it without supplies. These secret stores were held by three men, each of whom till the very last believed that he held the *only* secret store. In the end it turned out as he expected, and the food so laid by was a life-saver.

In 1952 Dean Smith was appointed the first full-time professor of physiology at University College, Khartoum, at the Kitchener School of Medicine, which became the University of Khartoum in 1956. During his eight years there he built up a first-class teaching laboratory with all the apparatus and facilities available to medical students in the United Kingdom. His teaching produced excellent results, and as an external examiner on two occasions I can testify that a pass in 2nd M.B. physiology in the University of Khartoum was fully the equal of a similar pass in a British university.

He was always interested in the students' welfare: he devoted much of his time to their residences, their games, and their personal problems. The affectionate response of the students to his interest in them was especially obvious in the first days of Sudan's independence, when, in the middle of nationalistic and emotional demonstrations, they were very alarmed in case their professor should leave them.

He found research interests all around him. During termtime he and his colleagues investigated the properties of scorpion venom by chromatographic, biochemical, and pharmacological techniques. Much of this is published and more is to come. In vacations Dean Smith loved to go on trek with his wife and small daughter or sometimes with a few of his students. His Land Rover laden with camping equipment and an assortment of spare parts has ranged over large areas of the Sudan. A competent mechanic, his breakdown troubles were soon solved. On these trips he was, of course, much in demand as a doctor, especially in the remote villages, and he was able, from his long experience of tropical diseases, to deal easily with these requests. More important, he was able to investigate on the spot the general problems of the public health of remote areas—such as endemic goitre, fluorosis, endemic gonorrhœa, and various disorders of nutritional origin. His findings were the subject of many reports to the Ministry of Health at Khartoum. He was also interested in hæmatology, especially in relation to kala-azar. On these treks it was necessary to shoot for the pot, and Dean Smith was a remarkable shot.

It was always a pleasure to see how warmly he was received and regarded by his Sudanese colleagues in both the medical and civil services. They clearly trusted and respected him, and undoubtedly this was helped by a lively sense of humour on both sides.

I like to think of him as a courageous, wise, warm-hearted friend, full of vitality, with an inquiring mind not intimidated by technical difficulties but with a modesty which tended to minimise his own scientific achievements."

A friend who acted as Visitor on behalf of the Examining Board in England to the faculty of medicine in Khartoum recalls that during his brief stay, each Visitor had an uninhibited opportunity of gaining an insight into Smith's work as professor of physiology and dean of the faculty. He continues:

"In him was found a man of rare qualities of heart and mind, selflessly dedicated to his work, and implicitly trusted by both colleagues and students. It was by virtue of this trust that he was able to perform so superlatively well his many difficult and responsible tasks, and to make so notable a contribution to the welfare of the faculty. Not only as dean and professor, but also as host will Visitors ever remember him. To stay in his Khartoum house, and to sit with him and his charming wife in their colourful garden in the cool of the evening, conversing or listening to one of his large collection of operatic records, was a delightful and unforgettable experience."

Appointments

COLE, G. V., M.C., M.R.C.S., D.O.: ophthalmologist (S.H.M.O.), Plymouth clinical area.

FORREST, T. R. W., M.R.C.S.: senior assistant M.O.H. (maternity and child welfare), Plymouth.

GIBBS, D. F., M.B. Edin., M.R.C.P.E.: assistant geriatrician (S.H.M.O.), Devon and Exeter clinical area.

GIBSON, MARY D., M.B. Edin., D.P.H.: deputy senior M.O. (maternal and child welfare), Bristol.

HAWKINS, T. D., M.B. Lond., F.F.R., D.M.R.D.: consultant in radiology (neuroradiology), Addenbrooke's Hospital, Cambridge.

NEWSHOLME, G. A., M.D. Cantab., M.R.C.P., D.M.R.T.: consultant radiotherapist, United Birmingham Hospitals.

QUANTRILL, D. W., M.B. Birm., D.OBST., D.P.H., D.T.M. & H.: senior assistant M.O.H., Brighton.

TAYLOR, D. G., M.B. Belf., F.R.C.S.: consultant in cardiothoracic surgery, United Sheffield Hospitals and Sheffield Regional Hospital Board.

Leeds Regional Hospital Board:

CHANDLER, G. N., D.M. Oxon., M.R.C.P.: part-time consultant in general medicine, Leeds and Wakefield area hospitals.

DOSSETT, J. A., M.D. Lond.: consultant in pathology, Leeds area hospitals.

DUKE, P. A., M.D. Glasg., M.R.C.P.E., D.P.H.: consultant in geriatrics, Halifax group of hospitals.

FITTON, E. P., M.B. Leeds, F.F.A. R.C.S.: part-time consultant in anæsthetics, Leeds area hospitals.

WILSON, GEOFFREY, M.B. Leeds, F.R.C.S.: part-time consultant in general surgery, Chapel Allerton Hospital, Leeds.

Notes and News

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names.

Approved name	*Other names*
Allylœstrenol	17α-Allylœstr-4-en-17β-ol Gestanin
* Allylprodine	3-Allyl-1-methyl-4-phenyl-4-propionyl-oxypiperidine
Chlorphenoxamine	1-*p*-Chlorophenyl-1-phenylethyl 2-dimethyl-aminoethyl ether Clorevan is the hydrochloride
Cyclopentamine	2-Methylamino-1-*cyclo*pentylpropane Clopane is the hydrochloride
Demethylchlortetracycline	7-Chloro-4-dimethylamino-1 : 4*a* : 5 : 5*a* : 6 : 11 : 12*a*-octahydro-3 : 6 : 10 : 12 : 12*a*-pentahydroxy-1 : 11-dioxonaphthacene-2-carboxyamide Declomycin
Isocarboxazid	3-*N*-Benzylhydrazinocarbonyl-5-methyl-*iso*-oxazole Marplan
* Levophenacylmorphan	(-)-3-Hydroxy-*N*-phenacylmorphinan
* Metazocine	1 : 2 : 3 : 4 : 5 : 6-Hexahydro-8-hydroxy-3 : 6 : 11-trimethyl-2 : 6-methano-3-benzazocine
* Norlevorphanol	(-)-3-Hydroxymorphinan
Phencyclidine	1-(1-Phenyl*cyclo*hexyl)piperidine Sernyl is the hydrochloride
Pheniprazine	α-Methylphenethylhydrazine Cavodil is the hydrochloride
Pheniramine	3-Dimethylamino-1-phenyl-1-2′-pyridyl-propane Trimeton is the maleate; Daneral is the *p*-aminosalicylate
* Piminodine	Ethyl 1-phenyl-4-(3-phenylaminoprophyl)-piperidine-4-carboxylate
* Proheptazine	1 : 3-Dimethyl-4-phenyl-4-propionyloxy-aza*cyclo*heptane
Pyrrobutamine	1-(4-*p*-Chlorophenyl-3-phenylbut-2-enyl)-pyrrolidine Pyronil is the phosphate
Sodium Anoxynaphthonate	Sodium 4′-anilino-8-hydroxy-1 : 1′-azonaphthalene-3 : 6 : 5′-trisulphonate Coomassie Blue
Tetrabenazine	3-*iso*Butyl-1 : 2 : 3 : 4 : 6 : 7-hexahydro-9 : 10-dimethoxybenzo[a]quinolizin-2-one Nitoman
Triparanol	2-*p*-Chlorophenyl-1-(*p*-diethylamino-ethoxyphenyl)-1-*p*-tolylethanol MER-29

* Narcotic substances which fall under International Conventions and are not available as therapeutic agents.

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Proprietary name	*Approved name*
Cavodil	Pheniprazine
Clopane	Cyclopentamine
Clorevan	Chlorphenoxamine
Coomassie Blue	Sodium Anoxynaphthonate
Daneral	Pheniramine
Declomycin	Demethylchlortetracycline
Gestanin	Allylœstrenol
Marplan	Isocarboxazid
MER-29	Triparanol
Nitoman	Tetrabenazine
Pyronil	Pyrrobutamine
Sernyl	Phencyclidine
Trimeton	Pheniramine

University of Cambridge

On July 5 the degree of B.CHIR. was conferred on the following:

M. I. J. Andrews, D. R. Bailey, A. J. C. Balfour, J. H. J. Bancroft, T. M. Barratt, J. S. R. Baxter, J. S. Bland, R. P. Boggon, D. J. Bradley, D. P. Brenton, A. F. A. Brown, Edward Byrne-Quinn, H. C. Cameron, Anthony Catterall, G. P. Clein, Eric Clow, R. J. Cockerill, R. A. F. Cox, K. W. E. Craven, Patricia H. Curry, A. O. Davies, J. W. H. Doar, R. S. W. Dowling, C. D. M. Drew, P. W. Dutton, A. R. Elkington, P. B. C. Fenwick, J. A. W. Fitzgerald, Shelagh M. FitzGibbon, K. J. Fox, R. M. Frew, D. L. Froggatt, J. R. Garnham, J. D. Geddes, Hatem Khalil Abu Ghazaleh, S. M. Gibson, D. J. P. Gray, N. J. Gross, Eileen Hardy, P. W. R. Harris, W. G. Hartfall, R. J. Heald, K. W. Heaton, Christopher Heughan, T. G. Hewlett, M. C. Holderness, J. H. Holland, W. F. G. Hulley, J. S. Kirkham, David Knight-Jones, Gabriel Lazslo, N. J. P. Lehmann, R. D. B. Leicester, F. C. Leyland, Cheng-Chuan Lim, A. A. McFarlane, A. W. McKenzie, D. B. Mackie, B. E. H. Maden, E. S. Marsden, F. P. Marsh, L. P. Martin, P. A. H. Millac, C. H. Mills, M. J. Mitchinson, T. F. Mortimer, J. M. Newsom Davis, P. J. F. Nicholson-Lailey, A. D. C. Norris, R. C. L'E. Orme, J. R. Parker, W. L. Parry-Jones, H. R. Patterson, J. H. Pennington, Jeremy Pilcher, Edward Platts, I. M. Rabinowicz, R. A. Randell, D. R. Redwood, I. D. B. Rennie, Peter Richards, Gillian M. Riches, S. O. B. Roberts, Bernard Rowe, S. J. E. Russell-Wells, J. D. Scobie, M. T. Scott-Kerr, A. T. Seaton, B. A. Senewiratne, J. H. Sheldon, D. E. Sibson, Brian Simpson, I. McD. Simpson, A. F. Smith, M. E. Snell, P. R. C. Steele, G. M. Sterling, T. J. H. Sweeting, B. J. Sykes, J. H. Taylor, D. F. E. Thallon, R. H. C. Vaux, G. D. Walker, Robert Warrington, J. P. Watson, M. M. Webb-Peploe, R. W. B. White, J. L. Wilkins, E. R. Williams, T. J. Willis, P. L. Wright, P. H. L. Worth.

Royal College of Surgeons of England

On Aug. 4 Prof. L. N. Pyrah was elected a member of the council.

University of Birmingham

The following degrees have been conferred:

M.D.—F. H. Kemp (with honours); J. C. Haworth.
Ch.M.—Frank Ashton (in absentia).
Ph.D. (in the faculty of medicine).—J. D. Cumming.
M.B., Ch.B.—Joseph Herbert (honours, second class); Oyinade Adedoyin Adenubi, Keith Arthur, Helen S. Atkin, T. C. Barker, D. M. Batty, Michael Baum, Pauline J. Begley, M. C. C. Bird, I. A. O. D. Brodie, Elaine K. Broom, M. J. Chamberlain, Barry Chance, P. J. Collis, P. J. Connop, M. J. Critchley, Robert Cruthers, M. H. Daly, Gladys E. Dixon, P. M. Ellis, E. F. Evans, Anne S. Fawkes, T. J. Fidler, T. R. Fisher, Marion Gillett, David Gompertz, J. M. Goodburn, Gloria A. Griffiths, J. D. Hamer, E. F. Evans, Anne S. Fawkes, T. J. Fidler, T. R. Fisher, Marion Gillett, David Gompertz, J. M. Goodburn, Gloria A. Griffiths, J. D. Hamer, Rosemary E. Harris, A. R. W. Harriss, L. P. Harvey, C. J. Hazledine, Michael Hedden, Rosemary E. Heron, J. A. Hickman, B. D. Hill, M. K. Howard, R. C. Hughes, John Hurst, Brenda James, Cecily A. Jenkins, S. A. P. Jenkins, J. M. Kay, M. J. Kestle, E. J. Knight, Jadwiga E. M. Krzysztoporska, Elisabeth D. McGuinness, Robin McMurdo, John Morley, R. D. Mumford, C. G. F. Munton, R. J. Oakey, Victor Babafemi Odunlami, David Oldroyd, J. L. Pearsall, J. H. W. Pexman, P. H. W. Rayner, Donald Riddoch, A. G. Ringer, Theresa O. Scanlan, C. J. Smallwood, Patricia A. M. Smith, Bryan Stone, J. R. Storer, Elizabeth A. Stubbs, Beryl O. D. Taylor-Lewis, J. F. Thompson, Christine C. Tong, P. J. Tovey, B. A. Wharton, P. J. Wheeldon, Pauline Whitfield, Barry Wilson, Anthony Worrall.

Medical Research Council

The Council announce that they have made the following travelling awards for 1960–61:

Rockefeller fellowships.—Dr. D. N. Baron, honorary consultant chemical pathologist, Royal Free Hospital, London; Dr. C. J. Dickinson, Leverhulme research scholar; Dr. R. W. Guillery, lecturer, anatomy department, University College, London; Dr. J. W. S. Harris, lecturer, department of anatomy, London Hospital Medical College; Dr. E. W. Poole, lecturer, department of clinical neurophysiology, Institute of Psychiatry, London; Dr. P. H. Wright, lecturer in chemical pathology, Guy's Hospital Medical School, London.

United States Public Health Service fellowships.—Dr. Harry Keen, lecturer and research fellow, department of experimental medicine, Guy's Hospital, London; Mr. S. J. Kilpatrick, lecturer in medical statistics, department of social and preventive medicine, The Queen's University, Belfast; Dr. J. D. H. Slater, medical registrar, department of medicine, Postgraduate Medical School of London; Dr. W. C. Watson, senior registrar, university medical unit, Glasgow Royal Infirmary.

Lederle fellowship.—Dr. Celia M. Oakley, registrar, department of medicine, Hammersmith Hospital.

Lilly fellowship.—Dr. M. T. Harrison, registrar, department of medicine, Hammersmith Hospital, London.

Alexander Pigott fellowship in ophthalmology and otology.—Dr. A. B. Leith, resident, Montreal General Hospital; Mr. C. I. Phillips, consultant ophthalmic surgeon, United Bristol Hospitals and South-Western Regional Hospital Board.

International Federation of Surgical Colleges

A meeting of the Federation is to be held at the Royal College of Surgeons of England on Oct. 18–20. The theme will be the Training of Surgeons, and the programme will include lectures, research communications, and discussions. Anyone who might like to attend all or part of this meeting is asked to write to the Secretary, Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, for further particulars and enrolment forms.

Gastro-enterological Symposium

The University of Birmingham is holding a symposium for consultants, senior hospital medical officers, and senior registrars, at the Queen Elizabeth Hospital, Birmingham, on Oct. 21 and 22. There will be three sessions—on steatorrhœa, gastro-œsophageal lesions, and lesions of the small and large intestine. Further particulars may be had from the chairman of the board of graduate studies, Dr. A. G. W. Whitfield, at the Medical School, Birmingham, 15.

Horder Memorial Prizes

The British Spas Federation is offering three prizes of £15 each for papers of original work relating to medical and/or social problems of rehabilitation. Further particulars may be found in our advertisement columns.

Births, Marriages, and Deaths

BIRTHS

PYKE.—On Aug. 9, at King's College Hospital, London, to Janet, wife of Dr. David Pyke, a daughter.